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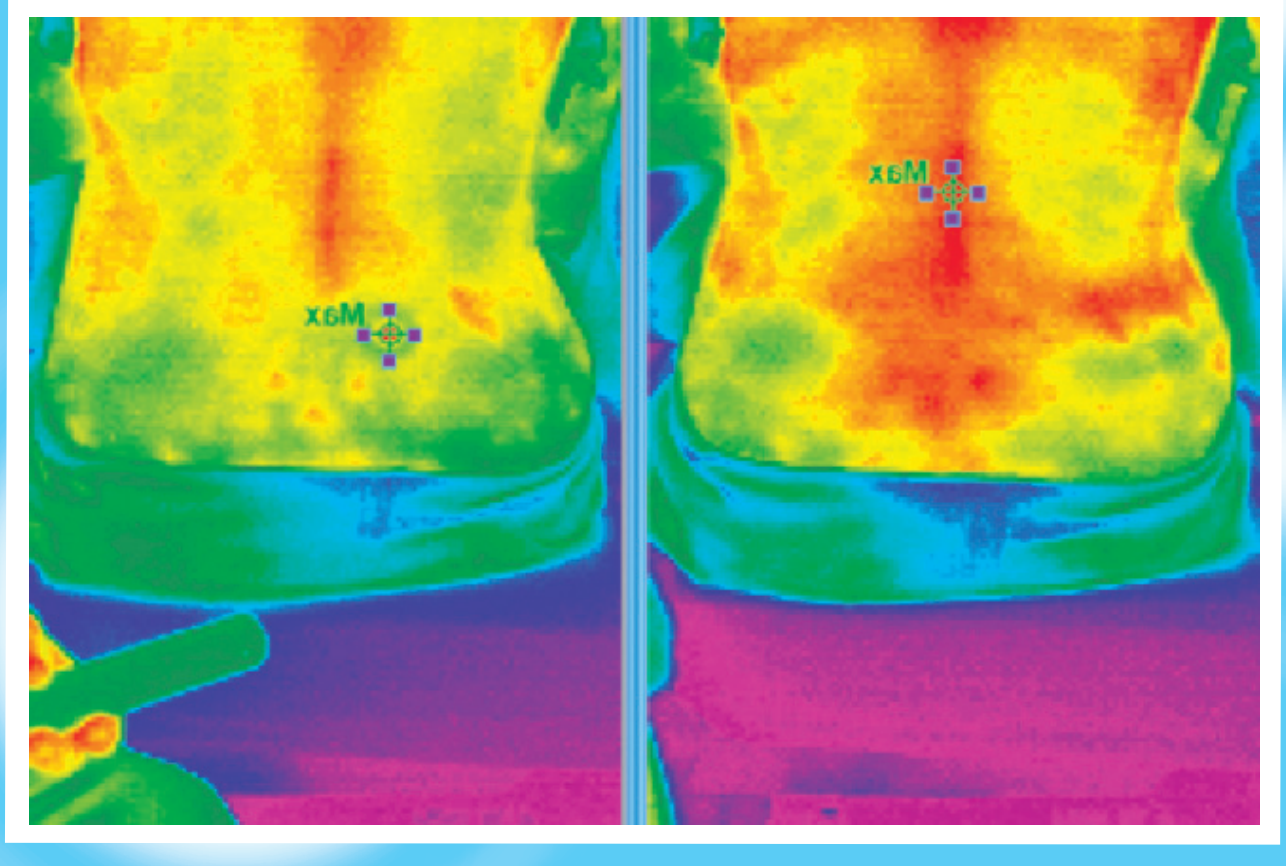

Patient with prostate adenocarcinoma T2N0M1 and Mt in LIII treated by external beam radiation therapy. Actinic dermatitis (at 1 month follow-up).

From the article on page 23

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Welcome to the Moldovan Medical Journal!

The journal was founded in 1958 on the initiative of Nicolae Testemitsanu, an outstanding expert in orthopedic surgery, social medicine and public health. From its debut the journal has striven to support the interests of Moldovan medicine concerning the new concepts of its development.

Since 2017 the owner of the journal has become the Scientific Medical Association of the Republic of Moldova and the journal continues to function as the scientific double-blind peer reviewed periodical edition issued 6 times per year designed for specialists in the areas of medicine, dentistry, pharmacy, social medicine and public health.

The Editorial Board warmly welcomes both the readers of and the authors for the journal, all those who are enthusiastic in searching new and more effective ways of solving numerous medicine problems. We hope that those who want to make their contribution to the science of medicine will find our journal helpful and encouraging.

CONTENTS

RESEARCH STUDIES

REVIEW ARTICLES

BOOK REVIEW

9 772537 637004 >

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RESEARCH STUDIES

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Femoral neck fractures in patients with stroke sequelae

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Abstract

Background: Patients with stroke associate a lot of complications; one of the most serious is femoral neck fracture. Nearly 30% of patients who have suffered femoral neck fracture die during the first year, in the survivors persists pronounced pain syndrome and reduced motility in the affected limb, and they become dependent in their habitual activities.
Material and methods: The notes of all patients with fractured neck of femur who were admitted to Clinical Hospital of Traumatology and Orthopedics, Chisinau, the Republic of Moldova, between January 2014 and December 2015 were scrutinized.
Results: In a series of 67 hemiplegic patients who subsequently fractured their hips, it was found that hip fracture occurred significantly more often on the hemiplegic side. Hip fracture was equally common in right and left-sided hemiplegia, and often occurred within five years of the stroke.
Conclusions: Hip fracture after stroke is an increasingly recognized problem. Measures to prevent bone loss and preserve bone architecture have not been part of stroke management thus far. Because rapid bone loss is a risk factor for fracture, we believe that kinesiotherapy in the early phase of stroke rehabilitation is indicated. If a successful prevention program could be worked out in stroke patients, there would be potential saving of lives, suffering, and resources.

Key words: stroke, femoral neck fracture, osteoporosis.

Introduction

Increased fracture risk is a recognized complication following stroke. Bone loss following a hemiplegic stroke has been proposed as a major risk factor for post-stroke hip fracture, with a recent focus on the development of novel therapeutic measures to prevent bone loss and fractures after stroke [10]. Stroke is a major cause of mortality and morbidity in elderly people. Information on the prevalence of stroke is difficult to obtain. However, it is expected to increase, because the incidence of stroke increases extensively with age and because survival after stroke is prolonged. Some of the risk factors for stroke, such as age and smoking, and for complications after stroke, such as paresis and immobility, are also well-known risk factors for osteoporosis. Other symptoms after stroke, such as reduced balance and perceptual disturbances, increase the risk of falls, which are common in stroke patients. Accordingly, stroke patients would be expected to be at risk for both osteoporosis and falls and, consequently, for fractures [1, 2, 3].

Stroke patients have up to a 4-fold increased risk of hip fracture, and poststroke hip fracture occurs late after stroke (median is 30 months after stroke onset) and most often affects the paretic side. The increased incidence of fractures after stroke is partly due to loss of bone mass in the paretic extremities after stroke, hemiosteoporosis, which begins early after stroke and continues to progress for the first years after stroke onset. The reported prevalence of previous stroke among patients with hip fracture ranges from 3% to 19%, but the prevalence has been studied neither recently nor over time.

Both stroke and hip fracture are common in the elderly but little has been written about the coexistence of these problems [4]. It is recognized that hemiplegic patients fall more often than other elderly people [5] and that such falls may result in hip fracture [6], so hip fracture can be a late complication of hemiplegia. Moreover, there is aclinical impression that hip fracture usually or invariably occurs on the hemiplegic side [7]. In order to determine whether hip fracture is indeed more common on the affected side, and to ascertain the interval between stroke and fracture, 67 patients with a history of hemiplegia who subsequently fell and fractured their hips were studied.

Material and methods

The notes of all patients with fractured neck of femur who were admitted to Clinical Hospital of Traumatology and Orthopaedics, Chisinau, the Republic of Moldova, between January 2014 and December 2015 were scrutinized. The admission history was studied to see if a completed stroke had occurred before the fracture. The side of the hemiplegia and the fracture and the interval between the 2 episodes were noted. All fractures were confirmed by radiography, and all patients underwent surgery involving internal nail fixation, prosthetic replacement. A previous stroke was defined according to the definitions of the World Health Organization as an "acute neurologic dysfunction of vascular origin with

sudden or at least rapid occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain," with symptoms lasting ≥24 hours. If the patient had suffered more than one stroke, the interval between the most recent stroke and the fracture was recorded. Patients were excluded if the fracture occurred before or at the same time as the stroke; if the patient had sustained bilateral strokes; and if the side of the stroke was not specified in the hospital notes.

Statistical analysis

Data were analysed by Microsoft Excel. We calculated average parameters, standard deviations; t-Student test was used for comparisons. A value of $p < 0.05$ was considered statistically significant.

Results

Evidence of previous hemiplegia was found in 67 patients. Four (6 %) of them had sustained 2 or more ischemic strokes. In 3 (4.5%) cases there were no residual signs of hemiplegia. There were 39 (58.2%) women and 28 (41.8%) men in the group of study. Mean age of patients was 67 ± 1,37 years (minimum 46 years, maximum 82 years), mean age of females was 68,8 ± 4,8 years and 60,8 ± 5,5 years for men. There was a significant difference in age between the men and women (p<0.001) (fig. 1).

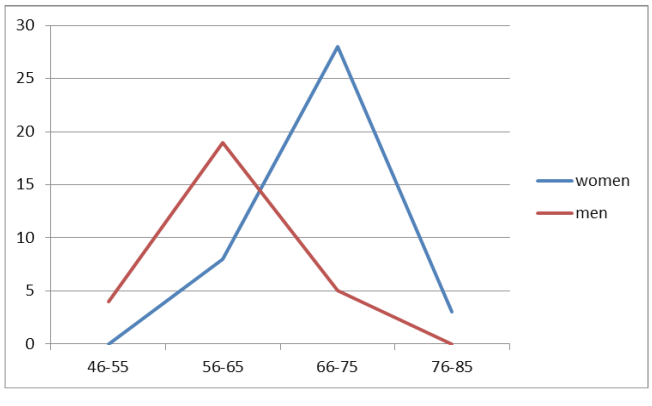

Fig. 1. Distribution on age.

All the women were aged 60 years or older, the majority (26 women, 67%) being in the 65-80 age range. Of the male patients, 6 (21.9%) were under 60 years, the youngest being 46 years old (tab. 1).

Table 1

The analysis variables in the group of study

	No	Mean age	The interval between stroke and fracture
Women	39 (58.2%)	68,8±4,8	4,3±2,8
Men	28 (41.8%)	60,8±5,5	4,9±3,5

Sixty four (95.5%) patients had sustained the fracture on the hemiplegic side, 3 (4,5%) on the opposite side (P<0.001). Patients with right and left sided hemiplegia were equally likely to sustain hip fractures (tab. 2).

Table 2

Side of hemiplegia and hip fracture

Side of hemiplegia	Side of hip fracture	No of patients
Right	Right	31 (46.5%)
Left	Left	2 (3%)
Right	Left	1 (1.5%)
Left	Right	33 (49%)

31 (46.3%) patients had sustained their fractures within 3 years of the stroke. The longest interval between stroke and fracture was 12 years (fig. 2). Only 2 patients fractured their hips within 6 months of the stroke. No patient was documented as having a stroke simultaneously with the fracture.

The prevalence of osteoporosis risk factors in the studied group was:

- Age: 65 patients (98.5%) were over 50 years,
- Gender: there were 39 women (58.2 %), all the women were over 50 years (100%),
- 11 smokers (16.4%) and 6 ex-smokers (8.9%) had been indentified, the average duration of the smoking cessation was 4 ± 1.36 years,
- 32 subjects were overweight (47.7%),
- 1 (1.5%) patient suffered from rheumatoid arthritis, and was on long-term glucocorticoid therapy
- 2 (2.9%) patients had neck fractures before.
- Heavy drinking was a preexisting risk factor to 6 (8.9%) of the subjects.

All patients underwent surgery involving internal nail fixation, prosthetic replacement.

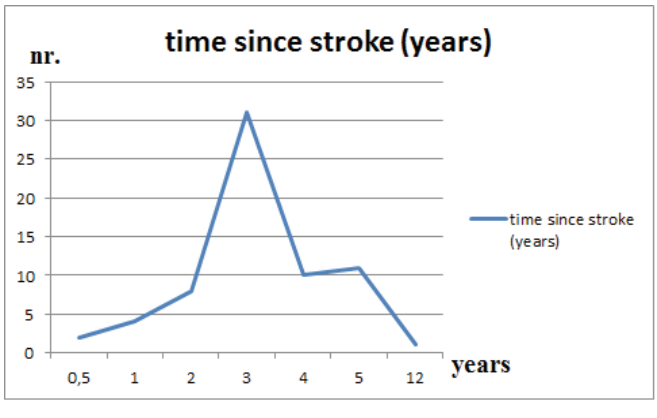

Fig. 2. Distribution by interval between stroke and fracture.

Discussion

In a series of 67 hemiplegic patients who subsequently fractured their hips, it was found that hip fracture occurred significantly more often on the hemiplegic side. Hip fracture was equally common in right and left-sided hemiplegia, and often occurred within five years of the stroke.

This study confirms the impression that hip fracture is significantly more common on the hemiplegic side. This may be because hemiplegic patients may tend to fall to the affected side [8], and the bone in the hemiplegic limb may be more

likely to break as a result of disuse osteoporosis [9].

There are many factors which contribute to the tendency of stroke patients to fall. These include sensory, motor, reflex and circulatory disorders [5]. Stroke may result in an upper motor neuron syndrome characterized by spasticity, muscle weakness, and a variety of motor control abnormalities that impair the regulation of voluntary movement. Spasticity may negatively affect balance, mobility, and gait, possibly increasing risk of falls and bone fractures. The problem is exacerbated by use of centrally sedating medications that have antispasticity effects-such as tranquilizers, calcium-channel blockers, and phenothiazines-but they predispose patients to an increased relative risk of falls when compared with patients not taking these medications. Appropriate management of spasticity is thus an important goal in the care of post-stroke patients, and may reduce incidence and cost of expensive and probably avoidable events such as falls and fractures. Spasticity is characterized by positive and negative symptoms. Positive symptoms include exaggerated reflexes, rigidity, dystonia, and flexor and extensor spasms that are often painful. Negative symptoms such as weakness, fatigue, and slow initiation of movement also occur. Contractures result when tonedependent joint restrictions on range of motion lead to deformity at the joint, requiring surgical intervention. Muscle weakness and loss of balance combined with hypertonia and other aspects of spasticity predispose patients to falls and fractures. According to the American Geriatrics Society Guideline for the Prevention of Falls in Older Persons, older patients with more than one factor predisposing them to fall are at a substantially increased risk for frequent falling. Generally, positive symptoms are more amenable to pharmacologic treatment than negative symptoms, but patients should have their medications reviewed as some agents have effects that may exacerbate fall risk.

There are some studies that show that patients with left-sided hemiplegia are particularly prone to perceptual disorders. They are less able to perceive verticality than are patients with right hemiplegia, they suffer, more commonly, from hemispatial neglect, also called hemiagnosia, which is a neuropsychological condition in which, after damage to the right hemisphere of the brain is sustained, a deficit in attention to and awareness of one side of space is observed [11, 12]. This study shows that right and left-sided hemiplegic stroke patients are equally likely to sustain hip fractures, which indicates that perceptual disorders are not important in the genesis of falls after stroke.

Changes in the locomotor function of the affected leg are believed to be responsible for most falls after stroke [5]. In patients with an equinovarus deformity of the ankle, the toe of the hemiparetic foot may catch the floor causing the patient to lose balance.

Patients with long-standing hemiplegia are known to develop disuse osteoporosis on the affected side. Literature data describe hemiplegic patients with unilateral osteoporosis who developed hip fractures on the affected side.

Several potential mechanisms contribute to bone mineral density loss after stroke, although there has been limited research into hemiplegia-induced bone loss at the cellular level [13]. A major factor is immobility, which contributes to generalized bone loss, in turn compounded by region-specific bone loss at sites such as the hemiplegic hip and upper limb.

Factors such as the duration of hemiplegia, degree of functional recovery, reduced vitamin D status and the use of anticoagulants [14, 15] may determine the rate and extent of bone loss after stroke. In a recently reported study of the changes in bone mineral density of the forearms and legs in relation to the duration of hemiplegia-induced immobilization after stroke, some studies confirmed that bone mineral density was decreased in the hemiplegic extremities relative to the unaffected side. They also found that there was an inverse relationship between duration of hemiplegia and bone mineral density values. In hemiplegic elderly patients with ischaemic stroke, hyperhomocysteinaemia has also been reported to be associated with hip fracture risk [16-30].

In the present study, only 2 patients sustained fractures in the first 6 months. In the early stages of recovery from stroke, one would expect those patients who had regained some mobility to be particularly prone to falls. The frequency of hip fracture in the first 6 months after stroke suggests that unilateral osteoporosis may be an important factor in the development of fractures in hemiplegic patients. Little is understood about osteoporosis in hemiplegic limbs. It would be interesting to know how commonly hemiplegic patients develop osteoporosis,how soon after stroke it occurs, and whether disuse osteoporosis is related to spasticity or weight-bearing.

The incidence of hip fracture after stroke is uncertain. Peszczynski in 1957 found that 23 of 150 patients attending a rehabilitation centre after hip fracture had a history of previous hemiplegia or transient hemiparesis [5].

Conclusions

In the present study, documentary evidence of previous hemiplegia was found in 67 patients. As the study is retrospective, it probably underestimates the incidence of hip fracture after stroke. Prospective studies are required to ascertain how commonly hip fracture occurs in hemiplegic patients, to determine the relative importance of the factors predisposing to falls and fractures in patients with stroke, and to decide whether specific rehabilitation methods are effective in reducing the tendency to fall and fracture bones on the hemiplegic side.

For the moment, a pragmatic strategy for a stroke unit might be to consider non-pharmacological measures such as adequate sunlight exposure, early physiotherapy and pharmacological measures such as vitamin D and calcium supplementation for hemiplegic patients, and also to develop effective technologies for prevention of falls. Prevention of falls, both during stroke rehabilitation and afterwards, is clearly of major importance in preventing hip fractures. An important

goal in the management of patients with spasticity involves restoration of normal limb position and ease of passive and/or active movement, with the aim of improving functional outcomes such as the ability to carry out activities of daily living.

So attention must be focused on stroke as a major and increasing risk factor for femoral neck fracture and also on the poor postfracture outcome and reduced survival of these patients. Prevention of poststroke fractures is necessary and is aimed at reducing the risk of poststroke fall and preventing the development of hemiosteoporosis.

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Predictive factors associated to low tuberculosis treatment outcome: cross sectional study

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Abstract

Background: The standard treatment for new case of drug-susceptible tuberculosis according to WHO recommendations in the Republic of Moldova has been performed since 2000 and must achieve a treatment success rate of at least 85%. Actually the treatment success rate has increased due to excluding of MDR-TB patients from the general cohort. The major rate of patients with low outcome is represented by died and lost to follow-up cases (drop out).
Material and methods: A retrospective selective, descriptive study targeting social, demographic, economic and epidemiological peculiarities, case-management, radiological aspects diagnosis and microbiological characteristics of 154 patients with pulmonary tuberculosis was performed.
Results: It was established that the major risk factors for loss of follow-up were: low educational level, homelessness, history of detention, migration and delayed patient's direct addressing the specialized hospital services. The major risk factors for death were: low educational level, homelessness and other ways of detection (detection by civic organizations, during specialized consultations in other somatic hospitals) as a result of the unemployment and lack of health insurance.
Conclusions: Raising awareness among high risk patients and their families about tuberculosis, emphasizing that the diagnosis and treatment are free of charge and independent regarding their social and economical status will improve disease outcome.

Key words: tuberculosis, risk factors.

Introduction

Tuberculosis represents a major global health problem, well recognized in the Republic of Moldova [1]. According to the WHO report in 2015, 10.4 million new cases were reported worldwide, of which 5,9 million (56%) were among men, 5.5 million (34%) among women and 1.0 million (10%) among children. From all new tuberculosis cases 1.2 million (11%) were people living with HIV. Two thirds of all cases were living in 6 countries: India, Indonesia, China, Nigeria, Pakistan and South Africa [2,3,4]. In the Republic of Moldova 4.211 cases were notified in 2015, 3.608 were new cases, 85% of them were tested by rapid diagnostic methods, 95% had HIV status, 90% had pulmonary tuberculosis and 64% were bacteriologically confirmed [1].

The standard treatment for new drug-susceptible tuberculosis according to WHO recommendations in the Republic of Moldova has been used since 2000 and lasts 6 months. It consists in a two phase regimen with four first-line drugs: isoniazid (H), rifampicine (R), ethambutol (E) and pyrazinamide (Z) in the intensive phase and two first-line drugs: isoniazid and rifampicine in the continuation phase [5]. It costs in average US$40 per person and must achieve at least 85% treatment success rate. In the top of causes of death worldwide tuberculosis was placed on the 5th place in lower-middle income countries in 2015 [6]. According to the WHO published data in 2014 in the Republic of Moldova the drug-susceptible treatment success rate in HIV-negative patients constituted 79%, in HIV-positive cohort 47% and in multidrug resistant tuberculosis (MDR-TB) cohort 53% [4]. The quality of TB control activities is demonstrated by the rate of MDR-TB cases at the regional level. Globally in 2015 there were estimated 580.000 new MDR-TB cases, but only 125.000 received DOTS-Plus regimen [4]. In 2015 in the Republic of Moldova 32 % (29%–34%) of new cases were MDR-TB and 69% (66%–72%) of retreated cases were MDR-TB [1].

The major determinants of tuberculosis treatment outcomes are socioeconomic inequalities in health [7]. Public health barriers which decrease treatment outcome are: geographic (long distance, natural barriers), economic (lack of social protection and medical insurance) and cultural barriers to health care access (stigma, poor housing and environmental conditions), malnutrition, harmful habits and substances abuse (tobacco smoking, alcohol abuse, illicit drug use), ethnic group affiliation and continuous contact with an infectious source [8,9]. In consequence, the distribution of low tuberculosis outcomes reflects the social determinants with impact on late disease diagnosis and treatment onset, poor treatment adherence and high rate of side effects [9, 10]. In comorbid groups the disease progression and low treatment outcome were determined by immune suppressive conditions: HIV-positive status [11,12,13,14], diabetes [15,16], cancer [17,18], silicosis [19], chronic respiratory diseases [20], gastrointestinal diseases, malnutrition [21], other immune suppressive causes (immune modulating drugs, immune suppressive therapy, antineoplastic drugs) [22,23,24,25]. The most relevant actions for improving the outcome in those patients must be performed in the frame of general medicine network, through the active screening and close follow-up of high risk groups [26,27]. In that subgroups the tight network between primary health care, tuberculosis specialized institutions and social services will ensure the highest treatment effectiveness [28].

There is a strong relationship between the investments in

activities for strengthening tuberculosis control programs, diagnostics, treatment and effectiveness of tuberculosis national policy. World Health Organization, International Union against Tuberculosis and Lung Diseases, and UNDP emphasized that interventions from outside the health sector, social protection and urban planning have the biggest potential to increase tuberculosis control. Those organizations recommend to pay attention and to solve social issues of tuberculosis patients [5]. Higher rate of low tuberculosis outcomes in disadvantaged groups such as in poor, comorbid, addictive groups and ethnic minorities demonstrated that inter-sector collaboration is underestimated and the community participation is unsatisfactory [29].

In the frame of supportive actions, there were established duties of the social worker to be performed within the National Tuberculosis Control Programme for assistance of tuberculosis patients, their families and other categories of population with risks: identifying their social rights, type of social assistance and services for promoting social support [30, 31]. Starting with obtaining and assistance in identifying documents for the local governmental social services, the patients will be assisted in registering in the list of the general practitioner, in establishing and maintaining a favorable partnership with authorities, municipality and non-governmental organizations. In association to the social security options, the psychosocial counseling and opportunities to get a free medical examination for tuberculosis and associated diseases must be provided [32].

According to the economical status of tuberculosis patients there are different possibilities for each patient to ensure a high quality adherence to tuberculosis treatment, that are more or less satisfied by the local municipality: financial assistance – food parcels, travel vouchers, financial support [33]. It was well recognized that only governmental-public organizations have no sufficient impact on the quality of care of tuberculosis patients and treatment outcome. So, all stakeholders must agree a strong partnership for improving disease control including health focused NGOs and other organizations oriented for serving poor communities, vulnerable subpopulations, ethnic minorities, migrant workers, etc. [32,34]. However, academic institutions, medical and public health schools, throughout the scientific programmes must provide technical support for analysis of health determinants, epidemiology and monitoring of high risk patients for establishing community-based health projects and improving tuberculosis treatment outcome.

So, the aim of the study was to assess the major determinants of low tuberculosis treatment outcome: death and loss to follow-up in the period 2014-2016. Objectives were: 1. Assessment of tuberculosis treatment outcome dynamics in pulmonary tuberculosis cases registered in Chisinau during 2011-2015. 2. Assessment of general, socio-economic and epidemiological risk factors of pulmonary tuberculosis patients with low treatment outcome (death and loss to follow-up). 3. Evaluation of case-management, diagnosis, radiological aspects and microbiological characteristics of patients with low tuberculosis treatment outcome (death and loss to follow-up). 4. Establishment of a method for the comprehensive evaluation of risk factors for low treatment outcome (death and loss to follow-up).

Material and methods

It was performed a retrospective selective, descriptive study targeting social, demographic, economic and epidemiological peculiarities, case-management, diagnosis radiological aspects and microbiological characteristics of 154 patients with pulmonary tuberculosis registered in Chisinau city. The electronic system for monitoring and follow-up of tuberculosis cases (SIME TB) was used for the patients' selection. Data were extracted from the statistic templates F089/1-e "Declaration about patient's established diagnosis of new case/relapse of active tuberculosis and restart of the treatment and its outcomes". Inclusion criteria were: age > 18 years old, new case of pulmonary tuberculosis, signed informed consent. New case is the patient never treated for TB or has taken anti-TB drugs less than one month. The investigational schedule included demographic, social and epidemiological data: sex (male/female ratio), age (distribution in age groups), demographic characteristics (urban/rural residence), educational level, socio-economic status (employed, unemployed, retired, disabled, student), health insurance status (lack or presence of insurance), migration and detention history, presence of high risks (close contact with an infectious source, comorbidities: HIV-infection, diabetes, psychiatric diseases, immune suppressive treatment), type of infectious cluster, health care seeking behavior, way of the patient's detection. All selected patients were diagnosed and managed according to the National Clinical Protocol 123 "Tuberculosis in adults". Enrolled patients were distributed in three groups: the 1st group – control group (1) was constituted of 57 patients successfully treated (cured) in the period 01.01.2016-31.12.2016, the 2nd group – study group (2) was constituted of 22 patients lost to follow-up in the period of 01.01.2013-31.1201.2016, the 3rd group – study group (3) was constituted of 75 patients died during the treatment in the period of 01.01.2014-31.12.2016. Statistic analysis was carried out using the quantitative and qualitative research methods. Statistical survey was performed using Microsoft Excel XP soft.

Results and discussion

According to the published data by the Moldovan National Centre for Management in Health during the period 2011-2015 it was registered an important mortality decline (with 12,3/100.000) in Chisinau: 2011 – 19,2/100.000, 2012 – 15,4/100.000, 2013 – 10,8/100.000, 2014 – 10 /100.000, 2015 – 6,9 /100.000 population. Due to the improving of the treatment quality, the rate of died MDR-TB patients is continuously decreasing: 2011 – 51.7%, 2012 – 47.2%, 2013 – 46%, 2014 – 34.6%, and 2015 – 23.2%. The treatment success rate increased (+33.7%) from 2010 to 2014 in the positive acid fast bacilli patients: 2010 – 45%, 2011 – 56.7%, 2012 – 57.5%, and in bacteriologically confirmed cases 2013 – 70.3%, 2014 – 78.7%. The treatment failure rate showed a sharp decrease

from 2010 to 2015 due to definition changes: 2010 – 26.9%, 2011 – 23.6% and 2012 – 18.2%. During this period of time all cases identified with MDR-TB and performing drug-susceptible treatment were considered therapeutic failure. Starting from 2013 patients with treatment failure were considered only patients with microbiological smear positive after 5 months of treatment. Actually the rate of treatment failure is very low: 2013 – 6% and 2014 – 2.8%. The rate of patients lost to follow-up decreased evidently: 2010 – 15.8%, 2011 – 16%, 2012 – 13.7%, 2013 – 9.3% and 2014 – 11.2%.

Clinical study established a similar sex distribution in the cured (the 1st group) and lost to follow-up group (the 2nd group), with male/female ratio=1,43/1 in the 1st group and 1/1 in the 2nd group. Comparing control group of cured patients (the 1st group) and died patients (the 3rd group) it was established a predominance of men in the 3rd group: 62 (82.6%) *vs.* 33 (58.9%) women, with male/female ratio=2,69/1. Repartition of the patients into three age groups, identified that the largest represented were 18-44 years old in all three groups. Comparing the groups it was established that the rate of young (18-44 years) patients, economical and reproductive active people predominated in the 2nd group: 19 (86.3%) *vs.* control group 32 (57.1%). Patients from the age groups >45years predominated in the 3rd group without achieving the statistical threshold. So, while distributing patients according to the biological characteristics it was argued that men and women had the same probability to be cured or to default the treatment, but men more frequently die due to tuberculosis.

Demographic distribution identified that all the enrolled patients were from the Republic of Moldova and in all groups there was a similar proportion of individuals from the urban and rural areas.

Table 1

Distribution of patients by demographic data

Indices	Sex Age Residence	CG (1) N=56 (P %)	LFUG (2) N=22 (P %)	DG (3) N=75 (P %)
Sex	Men	33 (58,9)	11 (50,0)	62 (82,6) ## •••
	Women	23 (41,1)	11 (50,0)	13 (17,3) ## •••
Age groups	18-44 years	32 (57,1)	19 (86,3) **	37 (49,3)•••
	45-64 years	13 (32,2)	2 (9,1)	29 (38,6) •••
	> 65 years	11 (19,6)	1 (4,5) *	9 (12,0)
Residence	urban	35 (62,5)	17 (77,3)	50 (66,7)
	rural	21 (37,5)	5 (22,7)	25 (33,3)

Note: Applied statistical test: paired simple T-test, P – probability; Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; – p<0.001; LFUG (2) compared to the died group (DG) (3) •• – p<0.05; •• – p<0.01; •••– p<0.001.

While distributing patients according to the economic status, it was established that employed persons, that are contributing to the health budget by paying taxes, health insurance policy and social taxes predominated in the 1st group (control) comparing with the study groups. Disabled patients in all three groups demonstrated that most of them had no social protection and financial income. Low rate of retired patients was due to the young age of selected patients. Students were in a very limited number. Unemployed patients were the majority of all three groups, but statistically predominated in the 3rd group. Health insurance represents the major condition for accessing health care in the Republic of Moldova. Patients without insurance predominated in all study groups comparing with the control one.

Table 2

Socio-economic status of patients with pulmonary tuberculosis

Economic indices	State	CG (1) N=56 *(P%)*	LFUG (2) N=22 *(P%)*	DG (3) N=75 *(P%)*
Stable	Employed	9 (16,1)	1 (1,3) **	3 (4,0) #
	Disabled	1 (1,7)	1 (1,3)	3 (4,0)
	Retired	7 (12,5)	3 (4,0)	6 (8,0)
	Student	2 (3,6)	1 (1,3)	0
Vulnerable	Unemployed	37 (66,1)	16 (72,7)	63 (84,0) #
	Lack of insurance	35 (62,5)	19 (86,4) ***	61 (81,3) #

Note: Applied statistical test: paired simple T-test, P – probability, Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001.

Considering these results, *mass media* must inform general population about full accessibility to all related diagnostic tools and specific treatment for tuberculosis is free of charge for all Moldovan citizens regardless of their health insurance and economic status.

Table 3

Distribution of patients according to the last graduate level

Educational level	Educational status	CG (1) N=56 *(P %)*	LFUG (2) N=22 *(P %)*	DG (3) N=75 *(P %)*
Illiteracy	No school attendance	0	5 (22,7) **	4 (5,3)
Primary level	Primary & general incomplete school	25 (44,6)	7 (31,9)	33 (44,0)
Secondary level	Completed general school	11 (19,6)	4 (18,2)	27 (36,0)##
	Professional school	15 (26,9)	6 (27,3)	8 (10,7) ##
Higher education	Superior studies	5 (8,9)	0	3 (4,0)

Note: Applied statistical test: paired simple T-test, P – probability; Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001.

Assessing the educational level it was established that most of the patients from all three groups graduated primary and general incomplete school. However, the completed general studies were more frequently identified in the patients from the 3rd group comparing with the control group and gradu-

ated professional school more frequently patients from the control group comparing with the 3rd group. Higher education was established in a limited number of cases. So, awareness and information about disease signs as well as education for risk reduction of persons with low degree of education are the most important tools that must be performed by the civil society organizations. Exposed data are revealed in the table 4.

Hierarchy of risk groups according to the widest rate of patients identified that the biggest impact on the developing of active pulmonary tuberculosis in all three groups determined the patient's vulnerable economic status and living in poor conditions. Extreme poverty (homeless individuals) was identified only in the study groups. History of migration during last year and history of imprisonment statistically predominated in the 2nd group. Low rate of family TB clusters affiliated to each investigated patient in all groups was due to the low quality of epidemiological cross-examination, rather than to the lack of closed (family) contacts. Patients with associated diseases were one third of the 2nd group and one half of the 3rd group. Comorbid patients statistically predominated in the 3rd group comparing with the 2nd group and control group. Among associated diseases, HIV infection was established in 3 (5.4%) cases of the 1st group, 4 (18.2%) cases in the 2nd group and 13 (17.3%) cases in the 3rd group. Diabetes was diagnosed only in 1 (1.7%) case of the 1st group. Chronic alcoholism was diagnosed in 1 case (1.7%) in the 1st group, 4 (18.2%) cases in the 2nd group and 16 cases (21.3%) in the 3rd group. Neoplasm was diagnosed only in1 (1.3%) case in the 3rd group.

So, the distribution of patients with pulmonary tuberculosis with different low outcomes established the primary target groups in frame of which must be performed awareness, education, and improvement of health behavior of social and economically vulnerable groups, comorbid groups, migrants and homeless people.

Table 4

Rate of high risk groups

	Risk groups	CG (1)	LFUG (2)	DG (3)
		N=56 *(P %)*	N=22 *(P %)*	N=75 *(P %)*
Social groups	Poor living conditions	32 (57,1)	15 (68,1)	52 (69,2)
	Homelessness	0	3 (13,6) *	16 (21,3) ###
	Migration	5 (8,9)	7 (31,8) *	3 (4,0) •••
	History of detention	0	3 (13,6) *	1 (1,3)
EG	Closed contact	11 (19,6)	1 (4,5) *	3 (4,0)
MBG	Associated diseases	8 (14,3)	6 (27,3)	34 (45,3) ### ••

Note: SG – social group, EG-epidemiological group, MBG-medico-biological group.
Applied statistical test: paired simple T-test, P – probability;
Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001; LFUG (2) compared to the died group (DG) (3) • – p<0.05; •• – p<0.01; ••• – p<0.001.

Studying case-management it was identified that general medical staff was involved in the detection of one half of the control group and lower rate in study groups. The rate of patients detected by the passive way based on the microscopic examination of the symptomatic cases was statistically higher in control than in study groups. The rate of high risk groups investigated through active screening was low in all three groups that demonstrated low disease control in vulnerable populations. Specialized medical staff diagnosed more frequently patients from the 3rd group comparing with the 2nd during interdisciplinary consultations. Direct addressing to the hospital specialized services was used more frequently by the patients from the 2nd group comparing with control and the 3rd groups, due to the lack of health insurance and lack of direct addressing to the primary health care sector. Other ways of detection predominated in the 3rd group comparing with the control one. It was used for diagnosis of patients hospitalized in somatic clinical hospitals and for detection of high risk individuals performed by the civic organizations.

Table 5

Case-management characteristics

Health level	Detection ways	CG (1)	LFUG (2)	DG (3)
		N=56 *(P %)*	N=22 *(P %)*	N=75 *(P %)*
PHC	Detected by GPs-symptomatic way	21 (37,5)	1 (4,5) ***	14 (18,7)#
	Detected by GPs -screening of HRG	7 (12,5)	4 (18,2)	2 (2,7)
Ambulatory specialized level	Detected by SP- symptomatic way	12 (21,5)	2 (9,1)	22 (29,3) ••
	Detected by SP-screening of HRG	1 (1,7)	1 (4,5)	1 (1,3)
Hospital level	Direct addressing	9 (16,1)	11 (50,0) ###	16 (21,3) •••
Other	Other ways	0	3 (13,6)	20 (26,7) ###

Note: Applied statistical test: paired simple T-test, P – probability;
PHC-primary health care, GPs-general practitioners, SP-specialist pneumophtysiologist.
Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001; LFUG (2) compared to the died group (DG) (3) • – p<0.05; •• – p<0.01; ••• – p<0.001.

Identifying the clinical radiological forms of pulmonary tuberculosis it was established that infiltrative opacities prevailed in the control group comparing with study groups. Appreciating clinical radiological forms it was established that the majority of cases had pulmonary infiltrative tuberculosis. Other radiological forms: disseminated tuberculosis prevailed in the 3rd group comparing with the 1st group and fibro-cavernous tuberculosis in the 2nd group comparing with the 1st group. Distributing patients according to the number of the affected lungs it was established that one lung was in-

volved in two thirds of the 1st and the 2nd group and both lungs were affected in two thirds of the 3rd group. Destructive forms of pulmonary tuberculosis were identified more frequently in the 3rd group comparing with the 2nd group. Extensive forms of pulmonary tuberculosis affecting 3 and more lung segments predominated in the 3rd group comparing with the 1st and with the 2nd group.

Table 6

Radiological characteristics

Parameters	Detection ways	CG (1) N=56 (P %)	LFUG (2) N=22 (P %)	DG (3) N=75 (P %)
Forms of TB	PIT	54 (96,4)	17 (77,3) *	57 (76,0) ##
	PDT	2 (3,6)	2 (9,1)	13 (17,3) ••
	FCVT	0	3 (13,6) *	5 (6,7)
Localization	1 lung	38 (67,8)	16 (72,7)	19 (25,3)) ### •••
	Both lungs	18 (32,2)	6 (27,3)	56 (74,7) •••
Features	Lung destruction	19 (33,9)	5 (22,7)	35 (46,7) •
	Extensive forms	5 (22,7)	6 (27,3)	45 (60,1) ### •••

Note: PIT- pulmonary infiltrative tuberculosis, PDT- pulmonary disseminated tuberculosis;
FCVT- pulmonary fibro-cavernous tuberculosis;
Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05; ** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001; LFUG (2) compared to the died group (DG) (3) • – p<0.05; •• – p<0.01; ••• – p<0.001.

Table 7

Microbiological features

Characteristics		CG (1) N=56 (P %)	LFUG (2) N=22 (P %)	DG (3) N=75 (P %)
Microbiological	Microscopic positive	28 (50,0)	5 (22,7) ***	20 (26,7) ### •••
	Culture positive	35 (62%)	6 (27,3) ***	16 (21,3) ### •••
	GeneXpert MTB/Rif positive	43 (76%)	12 (54,5) ***	34 (45,3) ### •••
GeneXpert MTB/Rif	Sensible	43 (100%)	8 (66,7)	26 (76,5)
	Resistant	0	4 (33,7)	8 (33,5)

Note: Applied statistical test: paired simple T-test, P – probability;
Statistically significant differences between: LFUG (2) compared to the control group (CG) (1) * – p<0.05;
** – p<0.01; *** – p<0.001; DG (3) compared to the control group (CG) (1) # – p<0.05; ## – p<0.01; ### – p<0.001; LFUG (2) compared to the died group (DG) (3) • – p<0.05; •• – p<0.01; ••• – p<0.001.

When assessing the laboratory features of the enrolled cured new pulmonary tuberculosis cases, it was identified that one half of patients were microscopic positive for acid-fast-bacilli, 35 (62%) were identified to have positive bacteriological results (culture on solid Lowenstein-Jensen ether liquid MGIT BACTEC). The sensibility to the rifampicine through GeneXpert MTB/Rif assay was established positive in the entire control group. Drug sensitivity testing identified mono-resistance to isoniazid in 1 patient, poli-resistance to isoniazid and streptomycine in 3 cases and monoresistance to streptomycine in 1 case. In the 2nd and the 3rd group only every fifth patient was microbiological positive, due to the short duration of hospitalization. In the 2nd group were identified 4 patients with MDR-TB and there were no patients with mono- and poliresistance. In the 3rd group were identified 2 patients with MDR-TB and there were no patients with mono- and poliresistance.

An important research outcome represents the relative risk (RR), odds ratio (OR) and attributable risk (AR) indices for identifying the priority interventions in the frame of specific subgroups for low outcome. In the table 8 were represented only risk factors and features which predominated and exposed statistical difference between lost to follow-up and control groups. It was established that major risk factors for loss to follow-up were: low level of education, patient's homeless state and history of detention, followed by the migration and direct addressing to the specialized hospital services due to the lack of referral general practitioner and other socio-economical vulnerable characteristics.

Table 8

Risk factors for loss to follow-up

Factors		Statistical indices RR	OR	AR%
Age	18-44 years	1,13-10,72	1,31-18,62	**33%**
Social economical features	Lack of insurance	1,08-1,82	1,05-15,04	**27%**
	Low educational level	2,83-6,51	N/A	**100%**
	Homelessness	2,67-5,82	N/A	**100%**
	Migration	1,35-5,01	1,34-17,51	**72%**
	History of detention	2,71-5,91	N/A	**100%**
Case-management	Direct addressing to the hospital	1,51-5,73	1,79-15,99	**68%**

Note: RR-relative risk, OR-odds ratio; AR-attributable risk, N/A-non available.

Table 9

Risk factors for death due to the tuberculosis progression

Factors		Statistical indices RR	OR	AR%
Demographics	Men	1,81 (1,14-2,86)	3,32 (1,49-7,41)	**29%**
Social economical	Unemployment	1,68 (1,05-2,69)	2,83 (1,25-6,46)	**21%**
	Lack of insurance	1,58 (1,03-2,45)	2,61 (1,18-5,78)	**23%**
	Low educational level	1,81 (1,54-2,11)	N/A	**100%**
	Homelessness	1,96 (1,64-2,35)	N/A	**100%**
Case-management	Associated diseases	1,75 (1,34-2,29)	4,97 (2,07-11,94)	**69%**
	Other way of detection	2,02 (1,67-2,43)	N/A	**100%**

Note: RR-relative risk, OR-odds ratio, AR-attributable risk, N/A-non available.

The next table reflects data assessing risk factors and features which statistically predominated in the group of died patients comparing with the control group. It was established that major risk factors for death were similar as with those that determined the drop up: low level of education, homelessness and ways of detection other than passive and active way according to the national policy, and unemployment that was associated to the social vulnerability.

Conclusions

The standard treatment for new case of drug-susceptible tuberculosis according to WHO recommendations in the Republic of Moldova has been performed since 2000, lasts 6 months, consists in a two phase regimen and must achieve a treatment success rate of at least 85%.

The treatment success rate increased in last 5 years due to excluding of MDR-TB cohort from the assessed cohort.

Actually, the major rate of patients with low outcome is represented by died and lost to follow-up cases.

Comparing the control group consisting of cured patients and the study group that dropped out it was identified that major risk factors for loss to follow up were: low educational level, homelessness and history of detention, migration and direct addressing to the specialized hospital services.

Comparing the control group consisting of cured patients and the study group of died patients it was identified that major risk factors for death were: low educational level, homelessness and other ways of detection (detection by NGOs, specialized consultations in other somatic hospitals) as a result of the unemployment and lack of health insurance.

Raising awareness among socially vulnerable groups and their families about tuberculosis, emphasizing that the diagnosis and treatment are free of charge and independent regarding their social status will improve treatment outcome and disease control at the local level.

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Cranial deformities as a risk factor in the harmonious development of oral and maxillofacial region

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Abstract

Background: There is no information about cranio-facial asymmetry among school children and the influence of this pathology on the quality of life.
Material and methods: The study presents a descriptive analysis of 3923 children ages 7 to 18 years. In this scientific work were involved three types of schools: 421 children from schools with severe neurological disorders; 2157 children from auxiliary schools with special educational needs; and 1345 children from pre-university schools. Buccal examination included the dento-maxillary analysis in three planes (sagittal, vertical, and horizontal) and cranial anatomical shape was examined for all children.
Results: In total 3923 children were examined, of which 632 (16%) were determined with cranial asymmetry. Among 2157 children from auxiliary schools for children with special educational needs 18% were detected with cranial deformities. In schools for children with neurological disabilities cranial asymmetries were detected in 44.18%, and in pre-unuversity schools 4.76 % were found with cranial deformities. A high incidence (twice more) of dental alveolar anomalies were found in children with cranial deformities, compared to those without deformities in the sagittal plane, 15.5% of children with cranial deformities were found with dento-alveolars anomalies and 7.84% in children without cranial deformation was (P<0.001). Similar results were found in the determination of occlusion anomalies in the horizontal and vertical planes.
Conclusions: The high incidence of cranial deformities was found among handicapped children and children from schools with special educational needs. A few children with cranial deformities were found among children from pre-university schools. It was proved that a high risk of dento-alveolar anomalies have children with cranial deformities.

Key words: cranial deformities, malocclussion, plagiocephaly, craniosynostosis, handicapped children.

Introduction

The first information about the anatomy, morphometry, the classification of the cranium deformities appears in the works of Herodotus and Halicarnassis, Chios, Hipposcratus. Since ancient times is known about the tendency to model skull shape with a view to improve the intelligence of personality. From other sources we learned that the trepanation of the skull was known in prehistoric times and was performed in medical and mystic purposes [3,4,5,14]. Cranial deformities problem is actual today and became particularly acute with the launch of the campaign "Back to Sleep" by US pediatricians association. If in 1974 it was reported an incidence of positional plagiocephalies of 1 from 300 live births, so in 1996 their incidence increased from 1 to 60 neonates [9,10]. The incidence of craniostenoses is reported constant: 1: 1000 newborns. Bruneteau and Mulliken, WojciechDec suggest an incidence of cranial deformities approximately 48% of all live newborns depending on the examination criteria [7, 11].

Significant and rapid increase in the incidence of cranial deformations generated new problems related to child development. Many authors show that children with cranial deformities have increased risk for development of pathological manifestations of neurodevelopment, risk for cognitive deficits or learning/language disabilities, otolaringological and ophthalmological problems, even cosmetic etc. [13,14,15,20]. Dane St. John and al. have shown in their study the connection between skull shape and position of the mandible. This study supports the clinical observation that the mandibular asymmetry in deformational posterior plagiocephaly is secondary to rotation of the cranial base and anterior displacement of the temporomandibular and not the result of primary mandibular deformity [19].

However, the vast majority of studies are carried out in child's early development period and there is almost no remote information on development of cranial deformities and changes made by this pathology. Sybill Dee Stock Naidoo, in their study shows that information is very poor and can not explain cranial deformities role in the development of a child during the school period [8]. Approximately all studies regarding the incidence, neurological development, otolaringological development, ophtalmological development etc. of children with cranial deformities found have not taken into account the socioeconomic position of patients [21, 24].

Trying to create a treatment plan for cranial deformities has generated very controversial opinions. While some authors consider the superiority of treatment by using the methods of orthopedic or surgical remodeling of the skull, others plead for self-remodeling of the skull or considered the skull deformity a minor cosmetic problem. In this area there are different opinions, which are probably caused by the lack of long-term studies [18,16,12,15,8,22,23].

Currently there is limited published data on the long-term observation of children with cranial deformities. The studies that are in the literature have been conducted with small numbers of participants and include patients in early stage of life. Health care providers have little evidence-based research to guide parents in treatment decision making for cranial deformities. There is a need to examine the differences in long term symmetry of the skull among school children who have cranial anomalies vs. whom have not that remains scarce and ill-defined.

Proceeding from the above, in this study we aimed to assess the frequency of cranial deformities in children of school age in the Republic of Moldova and make the analysis of dento-maxillary status of children with and without cranial deformities.

Material and methods

The study was made at the Department of oral and maxillofacial surgery of the Faculty of Dentistry of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, in the period 2012 - 2014. The study was included in the State Program with the title: the Oral Health of children in the Republic of Moldova. The aim of the study was to determine the presence of oral diseases, quality of child's life and factors that may influence the presence of oral diseases. The study involved specialists in pedodontics, orthodontics, neurosurgeon, pediatric neurologist, maxillafacial surgeon, together with the team of plastic surgeons from Wake Forest University, Weanstom Salem, USA. Examination of children was performed under the information agreement accepted by the department of bioethics of Nicolae Testemitanu State University of Medicine and Pharmacy. The study presents a descriptive analysis of 3923 children ages 7 to 18 years. In this scientific work were involved three types of schools: schools for children with severe neurological disorders; auxiliary schools for children with special educational needs; and children from pre-university schools. In the first group 421 children with disorders were examined: 50.9% girls, 49.1% boys. Children examined had mental retardation (F70-F79), cerebral palsy (G80 - G83), episodic and paroxysmal disorders (G40 - G47), sequelae of inflammatory diseases of the central nervous system (G09) neurotic disorders, stress and somatoform (F40 - F48), congenital malformations, deformations and chromosomal abnormalities (Q00-Q99), other diseases of the nervous system (G90 - G99).

In the second group 2157 children were examined, 63.2% boys, 36.8% girls. In this group we have included children from auxiliary schools for children with special educational needs. In the third group of study 1345 children were examined: 48.9% boys, 51.1% girls. In this category healthy children from pre-university schools were included. All children were examined in medical units of their schools. All staff of schools was present at the examining. Clinical examination was performed in accordance with the questionnaire prepared beforehand and confirmed by the department of bioethics of Nicolae Testemitsanu State University of Medicine and Pharmacy of the Republic of Moldova. This questionnaire included general questions (age, gender, locality, examined school category) as well as special (buccal examinaton and exrtabucal examination: head and neck region).

Buccal examination included the dento-maxillary analysis in three planes (sagittal, vertical, horizontal). In the sagittal plane protrusion changes of the maxilla and mandible were found, in the vertical plane: open or deep bite changes, and horizontally: the presence of unilateral and bilateral laterognathia. Examination standards were used for the diagnosis of malocclusions. The term normal occlusion includes minimal deviations from ideal parts that do not generate aesthetic and functional changes. To determine the maxilla and mandible relation, children were examined in well lit classes. The tools used for the examination of the oral cavity were wooden spatula of single-use and sterile gloves. Each patient was examined in two positions: with wide open mouth and teeth in central occlusion in a sitting position or in bed. School doctor, nurse and teachers participated in examinations. Data were recorded in questionnaires prepared beforehand. Extrabuccal clinical examination included determination of cranial form by inspection and palpation as simple, modest, direct and accessible methods. In this study all forms of cranial deformities, classified as plagiocephalies and craniostenoses were taken into account. Plagiocephalies were determined by ear flags asymmetry, unilateral bulging in front or occipital part, or both, narrow skull in vertical, horizontal or sagittal plane, according to the Argenda classification [1]. When examining some forms of cranial deformities, it was difficult to determine the position of plagiocephaly or craniostenosis, that is why they have been categorized in the intermediate group, called "other forms of deformities". When during clinical inspection children were determined with cranial deformities, a wig cap was placed on each participant, in order to confirm the presence of deformity [1,2].

The results were analyzed using Epi-info-2002 and Excel from the package Microsoft office. The data were interpreted as M ± m (average error) by means of the criterion t-Student. All statistical methods were obtained from the Statistics for Windows, version 6. The difference was regarded as conclusive when $p<0.05$ [31].

Results

In total 3923 children were examined, of which 632 (16%) were determined with cranial asymmetry. 12.4% of these children were found with cranial deformities of plagiocephaly type, 1% – with craniostenoses and 2.7% with other deformities. Out of 2157 children from auxiliary schools for children with special educational needs 18% were detected with cranial deformities. In schools for children with neurological disabilities cranial asymmetries were detected in 44.18% of 421examined children and in pre-university schools from 1345 children 4.76% were found with cranial deformities ($P<0.001$).

In total 3923 children were examined. 2157 of these children were from auxiliary schools for children with special educational needs, 421 from school for children with neurological disabilities, 1345 children were from pre-university schools. 632 (16%) of 3923 examined children were detected with cranial deformities. As a result of this study, it was found that the rate of cranial deformities is directly proportional to the nature of the examined school. We found statistically true that in schools for children with neurological disabilities 44.18% cases were found with cranial deformations, in schools for children with special educational needs – 17.71%, while in pre-university schools – 4% ($P<0.001$).

The Moldovan Medical Journal, April 2017, Vol. 60, No 2

Table 1

Cranial deformities in children

Type of examined school	Auxiliary schools	Schools for children with neurological disabilities	Pre-university schools	Total, n	Total %	
Children without cranial deformities	1775 82.29%	235 55.82%	1281 95.24%	3291	83.89	
Children with cranial deformities of craniostenosis type	25 1.16%	8 1.90%	7 0.52%	40	1.02	
Children with cranial deformities of plagiocephaly type	330 15.30%	|99 23.52%	56 4.16%	485	12.36	X^2 647.225 P<0.0001
Other deformities	27 1.25%	79 18.76%	1 0.07%	107	2.73	
Total n	2157	421	1345	3923		
Total %	54.98	10.73	34.28		100.00	

Cranial deformities of plagiocephaly type were found with an increased rate compared to craniostenoses and other deformities. Thus, cranial deformities type plagiocephaly skull were found 23 times more compared to craniostenoses. In schools for children with neurological disorders 23.52% of cases were deformities of plagiocephaly type, while 1.90% were craniostenoses, in auxiliary schools 15.30% of cases were plagiocephalies and 1.16% – craniostenoses, but in pre-university schools 4.16% plagiocephalies and 0.52% craniostenoses (P<0.001). In the present study we found that plagiocephalies of I, II, III degrees are most commonly encountered in all categories of examined schools being from 3.19% to 3.75% with a decrease in deformities of IV and V degrees (1.76% and 0.18%), (P<0.001), (tab. 1).

Table 2

Sagittal occlusion disorders

Cranial deformities Maxilla protrusion	Without n/%	With n/%	Total n/%	$X^2$37.769 P< 0.000
Present	258 7,84	98 15,51	356 9,07	
Absent	3038 92,16	543 84,49	3567 90,93	
Total	3291 83,89	632 16,11	3923 100	

Table 3

Jaw deformations in the sagittal plane

Cranial deformities Mandible	Without n/%	With n/%	Total n/%	$X^2$11770 P< 0.001
Absent	3225 97%	605 95%	3831 97,63%	
Present	66 2%	27 4,27%	93 2,37%	
Total	3291 83,89%	632 16,11%	3923 100	

After analyzing examinations of alveolar and dental systems, made in the three reference planes (sagittal, vertical and horizontal), it was found statistically true their increased rate, almost two times higher in children with deformities compared to those without cranial deformities. Dentoalveolar deformities in the sagittal plane – protrusion of the maxilla in children with cranial deformities was 15.5% and in children without cranial deformation was 7.84% (P<0.001). 4.27% of children with deformities were detected with the maxilla protrusion compared to those without deformities: 2.01%. So, it was revealed a high incidence (twice more) of dental alveolar deformities in the sagittal plane in children with deformities, compared to those without deformities (P<0.001), (tab. 2, 3).

Table 4

Horizontal occlusion disorders

Cranial deformities Open occlusion	Without n/%	With n/%	Total n/%	X^2 32.964 P< 0.0001
Absent	3115 94,65%	560 88,61%	3675 93,68%	
Unilaterally present	110 3,34%	43 6,80%	153 3,90%	
Bilaterally present	66 2,01%	29 4,59%	96 2,42%	
Total	3291 83,89%	632 16,11	3923 100	

Similar results were found in the determination of occlusion anomalies in the horizontal plane. Unilateral and bilateral laterodeviations were statistically true with a double frequency in the group of children with cranial deformities in comparison with those without (P<0.0001). Unilateral laterodeviations in children with deformities were 6% and bilateral deviations were 4.59%. While in children without cranial deformities, unilateral laterodeviations were 3.34% and bilateral were 2.01% (tab. 4). Dento-maxillar anomalies of open occlusion type were found in 11.71% of children with cranial defor-

mities and only in 5.59% of children without cranial deformities (P<0.001), (tab. 5). But we did not find this difference in disturbances of deep occlusion type (tab. 6). At the same time, we can say that the risk of development of malocclusion in the three planes is increased in children with cranial deformities).

Table 5

Vertical occlusion disorders

Cranial deformities / Deep occlusion	Without n/%	With n/%	Total n/%	$X^2$8464 P<0.0001
Present	693 21.06%	101 15,98%	794 20,24%	
Absent	2598 78,94%	531 84,02%	3129 79,76%	
Total	3291 83,89%	632 16,11%	3923 100	

Table 6

Vertical occlusion disorders

Cranial deformities / Open occlusion	Without n/%	With n/%	Total n/%	X^2 32297 P<0001
Absent	3107 94,41%	558 88,29%	3665 93,42%	
Present	184 5,59%	74 11,71%	258 6,58%	
Total	3291 83,89%	632 16,11%	3923 100	

Discussion

Studies with various aspects of cranial deformities are common worldwide. A multilateral analysis of this problem began in Moldova in 2004 with the establishment of a collaborative partnership and scientific cooperation between Nicolae Testemitsanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova, and Wake Forest University, North Carolina, Weanstom-Salem, between the departments of Head and neck surgery in children, neurosurgery, neurology and plastic surgery. During this period we have established the basis for plastic surgery in young children, as well as orthopedic remodeling of cranial relief with the help of wig caps donated by the team of plastic surgeons from the USA. This study was done on a group of 3293 children of school age who have not received treatment for orthopedic or surgical remodeling of the skull during early child development. As a result of statistical analysis we found that the frequency of cranial deformities constituted 16% of the examined children. Analysis of results showed high incidence of cranial deformities present among children with neurological disorders (48.18%). Almost a half of the examined children were found with cranial deformities. Their frequency was two times higher than in children from auxiliary schools for children with special educational needs (15.30%) and ten times higher compared to children from pre-university schools (1.16%). Deformities of craniostenosis type did not vary significantly in all groups of examined children and were much fewer compared to deformities of plagiocephaly type. Thus, in schools for children with neurological disabilities 23.52% of children had deformities of plagiocephaly type and 1.90% of children had deformities of craniostenosis type. Children from auxilliary schools with special needs had cranial deformities of plagiocephaly type 15 times more often compared with cranial deformities of craniostenosis type (15.30% versus 1.16%). The smallest gap was found in pre-university schools, where the prevalence of plagiocephaly deformities was only 4 times higher compared to craniostenoses (4.16% versus 0.52%) (P<0.001).

In the context that many authors establish a correlation between cranial deformities and high risk of development of neurological problems in these children [24,21,25] in this study we found that cranial deformities among handicapped children and those with special educational needs prevail compared to children from pre-university schools.

Some researchers in their study have demonstrated anthropometrical changes at the cranial base in children with cranial deformities [19,26]. Others have shown the changes in brain morphometry in magnetic resonance images [27]. In this study we found that along with changes in the cranial skeleton, neurological differences also persist at maxillo-dental level. Thus, the frequency of malocclusions in the three planes (sagittal, horizontal and vertical) is two times higher in children with cranial deformities compared to those without deformities, regardless the category of examined school.

Onyeaso C.O. determined that malocclusions among children from special schools are more common compared with healthy children [29]. Ana Cristina et al. tried to choose in their research the determinant factors of malocclusion in children with special needs [28]. At the same time, Bright Thilander et al. in their research have found a frequency of 88.1% of dentoalveolar abnormalities among healthy shool children [30]. Valentina Trifan notes an increased incidence of maxillofacial anomalies in the Republic of Moldova among healthy children [32]. In present study we found that the rate of malocclusions is two times higher in children with cranial deformities, than in those without cranial deformities.

Performing a literature study, we found that views on the indication, management, and period of treatment are very controversial. Saeed et al. found that deformities of plagiocephaly type do not require treatment and the skull self-remodels with age [17]. Plastic surgeons plead for orthopedic treatment, in comparison with pediatric neurosurgeons [12]. Sybill Dee Stock Naidoo in the study shows that it is difficult to demonstrate the efficacy of orthopedic or surgery treatment, as there are only a few studies on the long-term treatment outcomes [8]. So, as to the time of indicating the treatment or the self-modeling, opinions differ [22,23,24]. Present study demonstrates the increased risk of diseases of the maxillo-dental system in children of school age with cranial deformities and the higher incidence of cranial deformities among school children with special needs and handicapped children which requires appropriate treatment in cranial remodeling as early as possible.

Conclusions

Cranial deformities persist during school period of child's development. High incidence of cranial deformities was found in school children with neurological disabilities (48.18%), 2.5 times higher than in children from auxiliary schools with special educational needs (15.30%) and ten times higher compared with children from pre-university schools (1.16%). Cranial deformities carry an increased risk for dentomaxilar deformities in the three reference planes. High risk of cranial deformities to develop dentomaxilla anomalies, suggests the idea of orthopedic or surgical treatment of skull remodeling during early child period.

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Acupuncture, Moxibustion and Chinese herbs in prevention of nosocomial infection in patients with acute cerebrovascular accident

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Abstract

Background: Nosocomial infection is a current medical issue, particularly in patients with acute cerebrovascular accident. The present study purpose is to evaluate the effectiveness of acupuncture, Chinese herbs and moxibustion in prophylaxis of nosocomial infections in patients with acute cerebrovascular disease.

Material and methods: The study was carried out on a group of 100 patients. Valuing the efficiency of acupuncture, moxibustion and Chinese herbs in the prevention of nosocomial infections in patients with acute cerebrovascular accident, 50 patients (treatment group) with acute cerebrovascular accident received acupuncture and moxibustion treatment on points Zusanli (ST36) and Guanyuan (CV4) and per os – decoction Banqingheji. The control group (50 patients) did not receive any prophylactic treatment of nosocomial infection.

Results: In Acupuncture-moxibustion group infection rate was 2% (50/1) and 18% in the control group (50/9). In the control group were recorded 9 cases of infection, 7 cases (14%) constituted respiratory tract infections and 2 (4%) urinary tract infections. Acupuncture-moxibustion group revealed 1 case of respiratory tract infection.

Conclusions: Acupuncture, moxibustion on Zusanli (ST36), Guanyuan (CV4) points and decoction Banqingheji are efficient in the prevention of nosocomial infections in patients with acute cerebrovascular accident.The study demonstrates that in case of nosocomial infection of patients with acute cerebrovascular accident prevalent is nosocomial infection of the respiratory tract.

Key words: prevention of nosocomial infections, immunity, Zusanli, Guanyuan.

Introduction

Nosocomial infections have a long history and are associated with the occurrence of the first hospitals; they threaten not only the health and lives of patients but also cause huge economic loss for patients and society. The rate of nosocomial infections in different countries is 3%-17% [1]. The rate of nosocomial infections in the United States is approximately 5% [1], in UK is about 10% [2]. Nosocomial infections rate in China varies between 9.72–13.69% [2]. In Moldova, according to official data morbidity and lethality by nosocomial infections constitute respectively 6.5 and 2.0 per 1,000 people hospitalized [3].

The etymology of the word "nosocomial" (hospital) comes from the Greek word nosokomeion, nosos = disease and komeo = caring. At the beginning of the 19th century, it emerged the concept of transmitting infection from patient to patient and therefore in England appears first insulated four infected patients.

In the mid-19th century, Florence Nightingale in a study on military mortality remarked that: "The number of soldiers who died because of nosocomial infections is much higher than that of those who died in the war itself". Around the same time, Ignaz Semmelwei, Hungarian obstetrician, treating patients with puerperal fever noted that infection can be spread by medical staff in contact with the patient. And washing hands before and after consultation can prevent the spread of infection [4].

Nosocomial infection in the United States has brought increasing hospital expenses connected with 40 billion dollars per year [1]. In P. R. of China due to nosocomial infection hospital costs are increased by 10 billion yuan per year [5]. Field studies show that patients with nosocomial diseases pay for treatment 2489.89 yuan more than the patients who did not undergo a nosocomial infection and it increases hospital stay by an average of 15.68 days [6]. Currently in P.R. of China rate of nosocomial infections at patients with stroke constitutes 18.03%, at patients with hemorrhagic stroke – 29.30%, and at patients with ischemic stroke – 12.66% [7]. Clinical studies have shown that in patients with acute cerebrovascular accident prevailed nosocomial infections in the respiratory tract, so Wang Yan and Tan Jun [8] reported that the rate of respiratory infections was 6.96% (88/1265), the rate of urinary tract infections was 4.35% (55/1265), with other localization rate of infection was 1.11% (14/1265), the rate of infection with two or more locations amounted to 1.42% (18/1265). Pan Miao [9] reported that in patients with acute cerebrovascular accident, lower respiratory tract infection rate is 53.70%, 16.67% upper respiratory tract and urinary tract – 11.11%. Wang Fang and Yu Changqing [10] reported 73 cases of urinary tract infection, which is 67 cases (30,41%) of upper respiratory tract infections (27.92%), 59 cases of lower respiratory tract infections (24.58 %), 15 cases of infections of the gastro-intestinal (6.25%), 10 cases of biliary tract infection (4.17%), infections of skin and soft tissue infections – 9 cases (3.75%). The etiology of bacterial nosocomial infections in patients with acute cerebrovascular accident is so diverse, that Wang Yan, Tan Jun relate to them [8] 86 cases, including Pseudomonas aeruginosa – 25, 21 Escherichia coli, fungi – 13, 9 Klebsiella pneumoniae, Staphylococcus aureus – 8, Staphylococcus epidermidis – 6, Enterococcus – 4. Wang Fang,Yu Changqing [10] reported 155 cases of bacterial infection, in 35 cases was used the microbiological examination, as a result in 24 cultures were discovered gram negative bacteria which constitutes 62.50%, Escherichia coli 3, Klebsiella pneumoniae

2, Staphylococcus aureus 3, Staphylococcus epidermidis 3, Pseudomonas aeruginosa 3, Proteus mirabilis 2, Candida albicans 2, Citobacter 2, Enterobacter cloacae 2, Acinetobacter 1.

Zheng Xiaolan and coauthor [11] during eight years of clinical studies found that the percentage of G-infections decreased from 72.73% in 1997 to 52.54% in 2004 ($\chi 2 = 87.720$, <0.01). Rate of infections caused by Staphylococcus aureus is down from 15.31% in 1997 to 7.51% in 2004.

The main methods of nosocomial disease prevention are: disinfection, isolation and preventive use of antibiotics. But, in the case of prophylactic use of antibiotics, only 36% of patients showed clinical signs of infection, the prophylactic use of antibiotics in 24-57% was found to be unnecessary. Misuse of antibiotics has caused not only serious economic loss, but the occurrence of adverse events, the occurrence of antibiotic resistant strains as well as disturbance of the immune system of patients. Lederberg said: "People, to keep as a species, battle with the spread of nosocomial infections, causing the appearance of a large number of immunodeficient patients" [1].

According to relevant statistics, the rate of nosocomial infections in patients with a stroke is much higher than the average rate of hospital nosocomial infection [8-11]. Most patients with stroke are the people of the third age, with the decline of immune function; and the critical central nervous system damage, produces neuro-endocrine complications, worsening even more pronounced immune dysfunction. The need for a more invasive treatment increases the risk of infection. Thus, patients with cerebrovascular diseases have become patients at high risk of nosocomial infections, and prevention of nosocomial infections at patients with strokes became imperative.

Numerous studies have demonstrated the benefits of Traditional Chinese Medicine in prophylaxis of diseases. In the famous ancient medical work "Yellow Emperor" it is said: "If Qi Vital is rigorous, pathological factor can not act", also is mentioned the effect of acupuncture in strengthening Vital Qi, removing pathogenic heat and detoxification, and thereby obtain an immunomodulatory and anti-inflammatory effect.

Material and methods

The study was conducted in №1 University Clinic of the University of Traditional Chinese Medicine in Tianjin City, P. R. of China.

100 patients were randomly divided into two groups of 50 patients each. Both groups followed the conventional treatment of acute cerebrovascular accident. The research group in order to prevent nosocomial infection received Banqingtangji decoction 150 ml once a day for 6 days, followed by the treatment with acupuncture on Zusanli point (ST36) , and a bilateral Guanyuan point (CV4) plus Moxibustion on Zusanli points (ST36) during 15 minutes per day, for 6 days. The control group did not follow any prophylactic treatment of nosocomial infection. The observation period – three weeks.

Results and discussion

Following the prophylactic treatment of nosocomial infection applied in Acupuncture-moxibustion group infection rate was 2% (50/1) and 18% in the control group (50/9). In the control group were recorded 9 cases of infection, 7 cases (14%) constitute respiratory tract infections and 2 (4%) urinary tract infections. Acupuncture-moxibustion group had 1 case of respiratory tract infection.

Table 1

Comparison between 2 groups by age

Groups	40-50	50-55	56-60	61-65	66-70	71-75	Over 76
Acupuncture moxibustion group	2	9	6	6	9	8	10
The control group	3	2	4	9	9	5	16

(P>0.05)

Table 2

Comparison between 2 groups according to sex

Groups	Acupuncture-moxibustion group	The control group
Male	30	30
Female	20	20

(P>0.05)

Table 3

Ranking systems of nosocomial infection in the Acupuncture-moxibustion group

Localization	The number of cases	(%)
Respiratory system	1	2
The urinary system	0	0
Digestive system	0	0
Other locations	0	0

Table 4

Ranking systems of nosocomial infection in the control group

Localization	The number of cases	(%)
Respiratory system	7	14
The urinary system	2	4
Digestive system	0	0
Other locations	0	0

Most patients with acute cerebrovascular disease are elderly, because of illness and old age, the body's resistance is low, and the likelihood of infection increases significantly. Traditional Chinese medicine treatise lacks direct entries on the prevention of nosocomial infections, but two thousand years ago there was already the concept of disease prevention and "prevention and disease exacerbation". The treatise "Yellow Emperor" stated "if Qi Vital is vigorous, pathogenic fac-

tor can not act", so the state of Vital Qi is a decisive factor in the emergence of disease. Chinese medicine offers methods to strengthen Vital Qi respectively, regulating the immune response, effectively protected from infection, including the nosocomial ones. The basic components of Banqingtangji decoction are the following plants: Folium Isatidis and Radix Isadidis.

Table 5

Comparison of 2 nosocomial infection prevention groups

Groups	Ineffective	Total patiens(n)	Infection rate (%)
Acupuncture moxibustion group	1	50	2
The control group	9	50	18

Note: n-number of patients, (P<0.01).

Folium Isatidis plant has a cold nature, bitter taste, is distributed on the meridians of heart and lungs, removes heat and toxins, cools the blood and removes macules. In "Chinese Materia Medica" [12] it is mentioned that, Folium Isatidis plant: "Treats toxic fire and macules caused by pestilence, treats macules and papules caused by wind and heat treating intestinal ulcers and lung pain, stops hemoptysis and epistaxis. For patients with toxic heat is indicated using the juice of the leaves". Radix Isadidis has a cold nature, bitter taste, is distributed on the meridians of heart and stomach. It possesses detoxification effect, removes the heat, favors throat and cools the blood. Mostly indicated in febrile diseases, headache, rash, toxic heat retention. Folium Isatidis plant and Radix Isadidis both have cold nature, bitter taste, are distributed on the meridians of the heart, lungs, stomach, have detoxification effect, cool the blood, remove heat from the lungs, stomach and heart, so they are highly effective in infections.

Point name Guanyuan(,CV4) means: Guan – close, lock, store, and Yuan concerns Yin and Yang energies. This point is at the uterus level which is "Essence home". In the famous ancient work "Su Wen-Qi xue lun", it is mentioned that this point belongs to Ren meridian, above is the – Mu point of Small Intestine Meridian of hand Taiyang, also is the confluent of the Three Yin Meridians: Liver, Spleen and Kidney, is located on the midline, three cun below the navel. Nearby are abdominal veins and arteries, nerves ramifications, this area is called Dantian. Guanyuan point stores Premordial Essence and Qi (Yuan Qi). The area between the lower and kidney umbilical region is considered the home of the 12 meridians and life. The ancient works and contemporary studies point out the efficiency in the treatment of diseases of the urinary system, genicologic, reproductive disturbances, due to its function of regulating Qi and blood.

Ancient doctors appreciated very much curative action and health maintenance effect of the point Zusanli (ST36). This is the point – He of the Stomach meridian. In the ancient books it is said: "The stomach is the sea of five organs Zhang and the six organs Fu". "The stomach is the sea of water and cereals". Stomach interacts with spleen through the connection type interior – exterior. According to Chinese medicine theory bases, spleen is the postnatal source of life, the source of Qi and blood, vital based activities. In the ancient medical work it is said that, point Zusanli (ST36): "Controls stomach, controls distension and fullness of sensations in the abdomen and chest, controls decline of visceral Qi, constipation, abdominal pain, cardiac pain". Doctors in later generations summarized: point Zusanli (ST36) has beneficial effect on postnatal energy maintain pre-natal energy, regulates the function of the stomach and spleen, strengthens the body and prolongs life, is indicated for patients with chronic diseases including those with the immune system diseases. Clinical studies have demonstrated that moxibustion applied on Shenque point (CV8) has immunomodulatory effect by increasing values of IgA, IgM, IgG [13]. And moxibustion applied to Zusanli point (ST36) to patients with leukopenia resulted in increased values of IgA, IgM, IgG [14].

WanWenli [15] reported that moxibustion applied to Zusanli point (ST36) increases activity of RBC-C3bRR (red blood cell C3b roeetor rosette), increases CD4 values and decreases CD8 values. Immunomodulating action of points Zusanli (ST36) and Guanyuan (CV4) was investigated by Tang Shi [16] who reported that the application of moxibustion on points Zusanli (ST36) and Guanyuan (CV4) has an anti-inflammatory and immunomodulatory effect by suppressing cytokine release, strengthening the thymus, spleen, and by adjusting the imbalance of neurotransmitters – norepinephrine (NE) and serotonin (5-HT). Moxibustion action on T lymphocytes was investigated by HanCui [17], he observed antitumor effect of the method of moxotherapy "tianjiu" in mice with transplanted tumor. The study showed that the method of Moxibustion "tianjiu" inhibits the growth of solid tumors S180, inhibits weight gain of the spleen and decreases thymus weight. Moxibustion method "tianjiu" significantly increases the activity of T lymphocytes T and NK cells (Natural killer cells).

Zhao Jianguo [18] studied the effect of decoction Banqingheji in the prevention of nosocomial infections in patients with acute cerebrovascular accident. The study demonstrated that in the group that used the decoction Banqingheji efficiency ratio was 91.00% and in the group that used allopathic medicine efficiency ratio was 64.50%. Therefore, decoction Banqingheji by the effect of adjusting the immune function can be used in the prophylaxis of nosocomial infections.

Immunomodulating effect of acupuncture is holistic; this is one of the basic concepts of Chinese medicine. Acupuncture can operate simultaneously at different levels of several organs and organ systems. This action is realized by the hypothalamic-pituitary-adrenal and nervous system. Due to the holistic effect of acupuncture, it can act in two ways as a regulator; it may improve immune function and inhibit the hyperactivity to decrease immune system function. This adjustment in either direction is possible due to the close link between nervous, endocrine and immune systems [19].

Song Chunfeng [20] has found that Chinese herbs also

have a holistic effect, regulating the hypothalamic – pituitary – adrenocortical sistem, especially in cases of kidney deficiency, aging, stress, climacteric changes.

Most scientists believe that 33% of cases of nosocomial infection could be prevented [21].

Conclusions

1. Acupuncture and moxibustion applied on Zusanli (ST36) and Guanyuan (CV4) points in combination with BanQingheji decoction are effective in the prevention of nosocomial infections in patients with acute cerebrovascular accident.

2. In patiens with acute cerebrovascular accident prevails nosocomial infection of the respiratory tract.

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Infrared thermographic evaluation of patients with metastatic vertebral fractures after combined minimal invasive surgical treatment

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Abstract

Background: Vertebral cement augmentation and external beam radiotherapy have become increasingly used techniques for treatment of vertebral compression fractures due to spinal metastatic lesions in the Republic of Moldova. Surgically, the goal of vertebral cement augmentation is to improve the strength and stability of the injured vertebrae, as well as local tumor control. External beam radiotherapy for suppressing tumor or inducing pain relief are performed immediately after vertebral cement augmentation. Usually, local tumor control is occurred by CT or MRI studies. We have studied through the infrared thermography the dynamics of temperature gradient of tumoral foci skin projection.

Material and methods: The purpose of this study is to evaluate the local tumoral control, analyzing the infrared thermographic examinations in 33 patients with uncomplicated metastatic vertebral fractures, undergoing combined method of treatment (vertebral cement augmentation + external beam radiotherapy), before the treatment and at 12 months follow-up.

Results: We observed an indirect tumor "thermographic field" decrease registered by temperature gradient decrease from an average of 2.03±0.24°C in preoperatively to 1.28±0.33°C at 12 months postoperatively follow-up.

Conclusions: Combined method of stabilization (vertebral cement augmentation + external beam radiotherapy) in patients with uncomplicated metastatic vertebral fractures is effective in minimal invasive surgery and offering local tumor control.

Key words: spinal metastases, pathological fractures, vertebral cement augmentation, radiotherapy, infrared thermography.

Introduction

Historically, temperature has been proved to be a very good indicator of health [4, 5. 8]. Human, being a homeothermic mammal, is capable of regulating deep body temperature within a narrow range through a number of behavioral, metabolic and physiological processes. In this order, the entire homeothermic body can be divided into two parts: the inner core and the outer periphery. The human inner-core normal temperature is preserved within a narrow limit (approximately 36.2–37.5°C), regulatory mechanism being essential for normal functioning of all biochemical ways. In this regard, any change of core and peripheral temperature, by a few degrees in the same conditions, is considered as a clear sign of probable illness [2, 3, 7].

The first report of cutaneous temperature changes is described by Hippocrates and later by ancient doctor Celsius (Celsian signs). In 17th century, physician George Martin first used the thermometers to measure diurnal changes of temperature in normal subjects. In 19th century, Carl Wunderlich published his report, where he described temperature as a scientific indicator of illness. In 1800 was discovered, by Sir William Herschel, infrared radiation followed by the recording of the first thermal image, which opened new dimensions in the field of temperature measurement. Hardy, in 1934, described the physiological role of infrared emission from human body and proposed that human skin can be considered as a thermal radiator and established the diagnostic importance of temperature measurement by infrared technique which paved the way for using infrared thermography in medical sciences. But, the first use was reported just in the 1960, because of non availability of special quality equipment [1, 6, 7].

Infrared thermography (IRT) is a non-contact, and therefore remote, method of measuring the surface temperature of objects. All objects with temperature above absolute zero emit electromagnetic radiation, which is known as infrared radiation or thermal radiation, within a range of 0.75–1000 μm. The infrared emissions from human skin at 27°C lie within the wavelength range of 2–20 μm. It peaks around 10 μm. For medical applications, we use a very narrow wavelength band (8–12 μm). As per usual, the first modern infrared detector was originally developed for military applications [5].

The IRT examination of irregular objects surface causes abnormal thermal patterns, which indicate the presence of those defects. Similarly in clinical practice, the illness causes abnormal thermal patterns on the skin surfaces. In 1963, Barnes demonstrated that thermograms can provide information of physical anomalies and thereby be useful for diagnosis of physical illness [3, 6, 8, 9].

Material and methods

We analyzed the IRT imaging, in a group of 33 patients with uncomplicated metastatic vertebral fractures, undergoing combined method of treatment (vertebral cement augmentation + external beam radiotherapy), before the treatment and at 12 months follow-up. For IRT imaging we used the portable hardware ИРТИС-2000 ME™. This device has been specially designed for use in medical practice, with a spectral range between 3-5μm, and a thermal range from -10°C to 170°C, with sensitivity in the field of examination of 0.02°C and accuracy of ±0.5°C.

The distance and angle of the subject to the camera have profound effects on the accuracy and precision of temperature measurement by IRT. In our study the IRT examination

The Moldovan Medical Journal, April 2017, Vol. 60, No 2

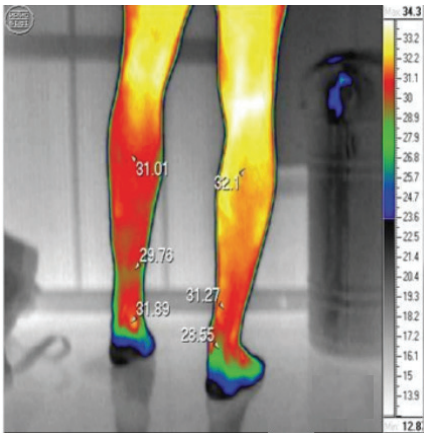

Fig. 1. Patient with breast carcinoma and L_{III} metastatic vertebral collapse with symptomatic radicular dysfunction.

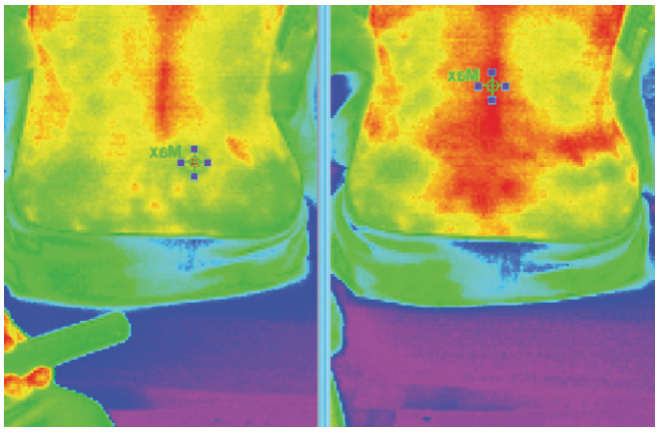

Fig. 2. Patient with prostate adenocarcinoma T2N0M1 and Mt in LIII treated by external beam radiation therapy. Actinic dermatitis (at 1 month follow-up).

was carried out in a room about 20m^2, with a temperature control about 20-24°C, convection and air leakage rate less than 0.4m/s and relative humidity 50-75%, in a comfortable position for the patient. For patients with severe static and dynamic disorders sitting in the chair or horizontally it was possible to record. The distance between the patient and analyzer was about 2-2,5m. The first record of IRT occurred after patient's adapting with room environment (average 10 minutes). It was registered thermal field over the tumoral locus in the spine, at the spinous line. If on the patient was observed any neurological disturbance, we registered thermal schedule over paravertebral lines and limbs. To appreciate the difference in temperature between the thermal projection of the vertebral tumoral locus and other anatomical regions of the examined patient was established standard thermal schedule or physiological status.

As a physiological status of the investigated patient served arithmetic average of IRT registered temperatures in eight different symmetrical anatomical regions of the body, in two points on the thorax and abdomen, respectively, and four points on the back. To determine the thermal activity (aggressiveness) of the metastatic locus in the vertebral segment, or severity of neurological deficits, we estimated stroke IRT. This is a functional pharmacological active test, registered after 30 minutes of sublingual administration of five pills of glucose with vitamin C. At the same time, we must keep in mind that, in the elderly it was impossible to rule out the influence of preexisting degenerative changes of the spine or peripheral vascular disorders on thermographic picture of the patient.

By these reasons, for the analysis and the correct description of the results obtained in the examination of the IRT, we used three basic principles:

- Thermo-morphological – describing the anatomy of the hyperthermic locus: location, shape, surface, contour, uniformity;
- Thermo-functional – represented by difference between background temperature and provoked temperature range of the tumoral locus, or body thermo-asymmetry (with temperature gradients definition);
- Thermo-regulation – functional tests were used for assessing the dynamics of thermal changes in tumor foci.

After the IRT examination was calculated temperature gradient (TG) by using the accompanying software of ИРТИС-2000М˜, which represents the difference between the maximum temperature (t°C) of the tumor field and standard thermal regime of the patient.

Results

Preoperative evaluation of patients in 100% cases revealed a typical thermal syndrome. It was represented by a clear hyperthermic area in tumoral field (over 1.5-2°C) with homogeneous irregular contour, sometimes asymmetrical, located in the projection of the vertebral tumor foci. In patients with symptomatic radicular syndromes, "root strips" were observed, represented by hypothermia zones on the affected limb as compared to the healthy limb (fig. 1).

After minimal invasive surgical treatment of collapsed vertebrae, we determined the thermo-functional characteristics of tumoral foci and limbs and we observed in follow-up the dynamics of TG after undergone therapy (fig. 2).

The efficacy of applied combined surgical treatment was tested in follow-up – before and after surgery at 1, 6 and 12 months. Were considered as positive results of the applied treatment the situations where the hyperthermic areas of tumor foci appear through a "model of extinction" in follow-up or hypothermic zones of limb occur through temperature normalization. In the absence of positive dynamics, we can consider tumor resistance or inefficiency of practiced method of treatment, which requires radical therapeutic model changes.

Thereby, after TG values registration, we obtained the values of temperature gradient in tumoral foci: before treatment – 2.03±0.24° [1.6°; 2.5°]; at 1 month – 1.98±0.3° [1.5°; 2.8°]; at 6 months – 1.55±0.28° [1.1°; 2.3°]; at 12 months – 1.28±0.33° [0.8°; 2.3°] (fig. 3).

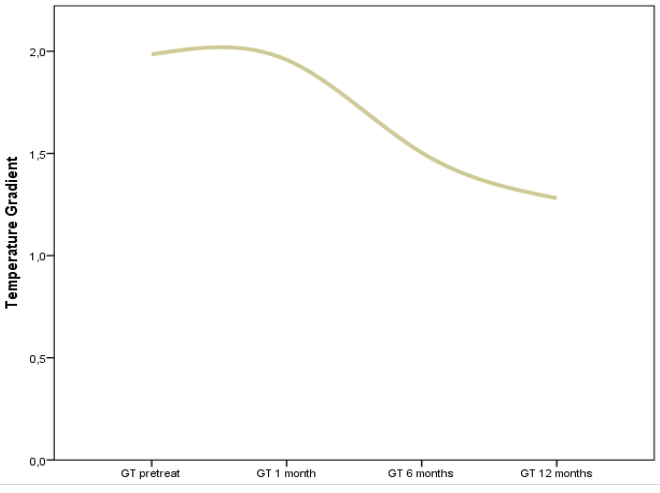

Fig. 3. Temperature gradient evolution in follow-up period.

Analyzing the data presented in figure 3, we observe that after applied combined method of minimal invasive surgical treatment, there is a general improvement of temperature gradient in tumor foci with -0.7±0.26° at 12 months.

Discussion

The human body's temperature is maintained constantly by a sophisticated thermoregulatory center in the hypothalamus. Thermoregulation is impaired in sick patients. IRT indicates the temperature pattern to identify an abnormality. Hence, there is no radiation risk as it captures the infrared radiation from the skin and is totally painless. Based on this idea, thermography was developed and first used for the diagnosis of breast cancer.

Because of its accuracy, low risk, and noninvasive nature, IRT should be employed as a cost-effective initial screening procedure to distinguish between patients with substantive radicular disorders and those experiencing minor localized injury. IRT is a test advocated by some physicians and chiropractors for diagnosing disk abnormalities.

Usually analysis of the thermograms of patients showed regional hyperthermia in the spinal pathology field and hypothermia in affected lower limb. The combination of local (spinal) and distant (peripheric) thermoasymmetries, which are realized through reflex mechanisms of vegetovascular innervation, is a characteristic feature of the thermovision syndromes in IRT examinations in patients with spinal disorders. The mechanisms of the origin of thermoasymmetry are discussed. For example, malignant cancerous lesions (neoplasms) develop high metabolism and use more blood supply than normal tissue. A comparative estimation of different methods in the differential diagnosis indicated the advantages of IRT. Several studies have found good to excellent reproducibility for paraspinal thermal scanning using a variety of devices [12-14].

Infrared thermography has become a reliable clinical technique used to measure body temperature and indicate noninvasively the presence of cancerous diseases. From these reasons, IRT can detect temperature changes during spinal diseases, also vertebral tumors.

This abnormality in temperature distribution might indicate the presence of an embedded tumor. Although, IRT currently is used to indicate the presence of an abnormality, there are no standard procedures to interpret these and determine the location of an embedded tumor [15-17].

Our research focused on the spinal tumoral field evolution before treatment and in follow-up. The temperature emitted from the skin visualized on the screen in the form of contoured color spectrum - blue, yellow, green and red - depending on "thermal activity" of vertebral metastases. The regional thermal deficit of the affected lower limb did not follow the specific dermatome. A possible explanation of this clinical finding is that blood supply of the skin in the lower extremities is different to the neural sensitivity in the same areas.

Studies on the application of thermography in spinal metastases management are scarce, and there are no studies of thermal changes during vertebral metastases evolution after cement augmentation. This research is a first step towards IRT examination outcomes of patients with spinal metastases after minimal invasive surgical treatment.

The main limitation is the absence of a control group. In future research, we will consider this. We believe that it has not significantly affected our results, because we analyze the absolute value of the temperature, but not the temperature difference between the two sides of the lower extremities.

Conclusions

By detecting cutaneous temperature changes in the tumoral foci, fracture level and limb, infrared thermography offers another non-invasive, contrast-free option in functional assessment of treatment outcomes. Percutaneous vertebral cement augmentation is a minimally invasive procedure and, when combined with radiotherapy, is effective in providing a local tumoral control.

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Intrauterine growth restriction: contemporary issues in diagnosis and management

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Abstract

Background: Intrauterine growth restriction represents a fetal life treating condition in obstetrics. Diagnosis and appropriate management during pregnancy is essential because of the considerable morbidity and mortality to which restricted new-borns are exposed. Implementation of diagnostic criteria could potentially determine an optimized outcome in these patients.
Material and methods: The article reflects a study of 728 cases of patients delivered to the Obstetrical department of Municipal Hospital No1, Chisinau, the Republic of Moldova during January-December 2016. A special protocol for clinical and paraclinical data collection was used. From these 728 cases, 50 histories of low birth weight fetuses (<2500g) were analysed in detail.
Results: The average weight of LBW fetuses was 2057 gr. 27 fetuses (54%) were diagnosed as intrauterine growth restricted fetuses. The average weight of fetuses with the diagnosis of IUGR was 1989 gr. 18.52% infants had a very low birth weight (1000-1499 g.), 84.48% infants had low birth weight (2500-1500 g).
Conclusions: The prevalent criteria for diagnosis of intrauterine growth restriction in our study were foetal abdominal circumference below 10th percentile (52.3 %). The ultrasound evaluation showed to have an average sensitivity in the predicting the foetal weight at birth (47.6%). In the majority of cases the delivery was done by cesarian section (62.9%), with the most frequent indication for foetal extraction – vascular redistribution and beginning of cerebral vasodilatation (37.5 %).

Key words: intrauterine growth restriction, small for gestational age, foetal Doppler, foetal biometry.

Introduction

Intrauterine growth restriction is a major public health problem both in the industrialized and developing countries. For obstetricians – gynaecologist's foetal intrauterine growth restriction means important risk for iatrogenic prematurity, foetal distress, impaired neurodevelopment, cerebral palsy and perinatal death [1]. The prognosis in neonatal intrauterine growth restriction depends on the severity of the etiological factors, presence of foetal prematurity, foetal distress, cerebral anoxia, perinatal asphyxia and meconium aspiration syndrome [2]. Diagnosis and appropriate management during pregnancy is essential because of the considerable morbidity and mortality to which restricted new-borns are exposed. Not to diagnose an intrauterine affected foetus means to jeopardize its vital prognosis. On the other hand, to deliver the foetus before term is to induce the risc of prematurity. The clinician is always measuring risk of delivery in very early gestation with associated morbidity against the risk of fetal death if the fetus remains in utero [3]. Conversely, to label a normal foetus by mistake as being growth restricted means to expose him to unnecessary interventions.

Thus, antenatal detection of intrauterine growth restriction and correct clinical management can improve outcome for these neonates. Also, we have to mention that till now, no evidence-based management protocols are available [4].

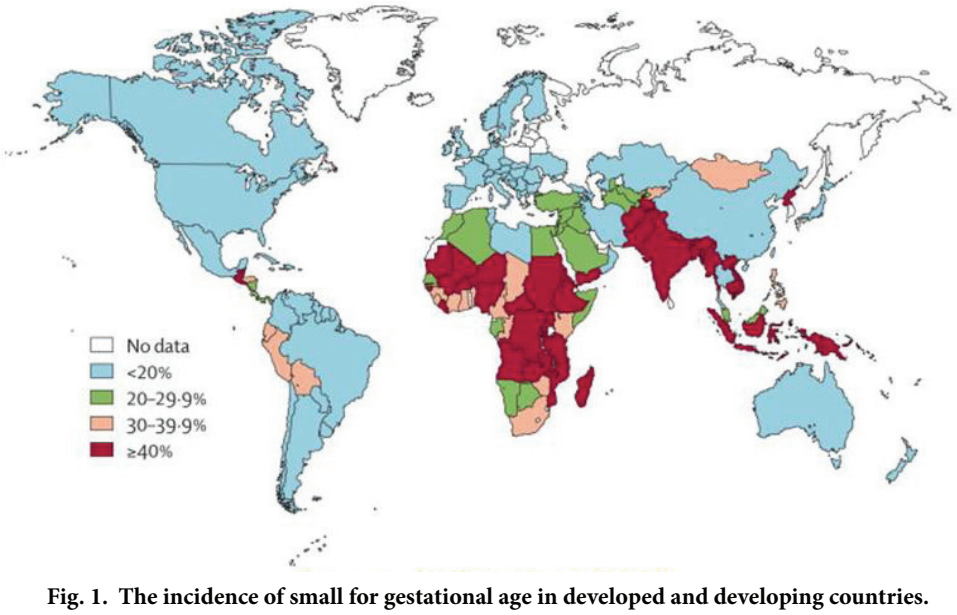

Fig. 1. The incidence of small for gestational age in developed and developing countries.

The Lancet in 2008 reported the incidence of foetal growth restriction in developed countries is 3-7% of birth, while in developing countries is up to 24-40% of cases [5] (fig.1).

In the Republic of Moldova the reported incidence is 6.3 ± 0.063% [6]. Normal fetal growth is determined by a number of factors. These include genetic potential, nutritional status of the mother, placental function and transfer of nutrients, and intrauterine hormones and growth factors. Numerous risk factors for foetal growth restriction have been described and classified into maternal, foetal and placental factors [7] (fig. 2).

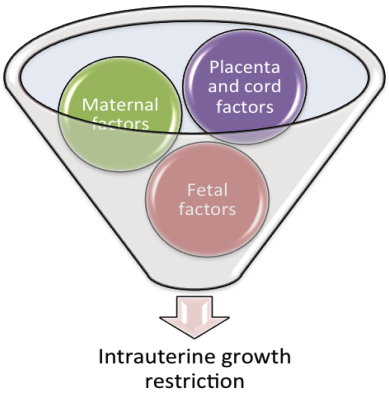

Fig. 2. Risk factors for fetal growth restriction.

Various maternal factors may lead to foetal growth restriction – under-nutrition hypertension, diabetes, anti-phospholipid syndrome, lupus erythematosus, hemoglobinopathies, maternal infections, chronic illness, drug abuse and drug exposure, smoking [8]. Foetal genetic syndromes and chromosomal disorders – trisomies 21, 13 and 18 and Turner's syndrome are associated with higher rates of growth restriction [9]. Placental and cord anomalies- membranous cord insertion, placenta praevia are associated with higher rates of foetal growth restriction. Among all causes, uteroplacental insufficiency is thought to be the major cause of intrauterine growth restriction [10]. The literature includes several confusing and controversial terms and definitions related to intrauterine growth restriction. There is no universally accepted definition of intrauterine growth restriction and most statistics include such terms as "small for gestational age", "low weight at birth", "very low weight at birth". These also include distinctions between 'references' used by the obstetricians, and those used by the paediatricians. In general, small for gestational age is defined as a birth weight below a certain limit compared with a population-based reference curve, while intrauterine growth restriction is defined as a failure to reach the genetic growth potential and always implies pathological growth [11]. For both "small for gestational age" and intrauterine growth restriction fundal height measurement is a screening method. This investigation has little ability to differentiate between normal but small fetus and the fetus at perinatal mortality and morbidity [12]. There are no universally accepted criteria for the diagnosis of abnormal foetal growth. Obstetrical literature as diagnostic criteria proposes: a) a fall in symphysis-fundus curve; b) deviation in ultrasound fetometry; c) pathological Doppler examination of the umbilical artery in small for gestational age fetus; d) pathological amniotic fluid volume in small for gestational age fetus [13]. The current gold standard for the diagnosis of abnormal foetal growth remains biometry: the most used definitions are based on abdominal circumference or calculated foetal weight for a given period of gestation below the 10th percentile [14]. Till now, there is no consensus on whether the diagnosis of intrauterine growth restriction, should be based on estimated foetal weight, estimated abdominal circumference or both [14, 15, 16].

Material and methods

The article reflects a descriptive, non-experimental study with a general group of 728 patients hospitalized during 2016 in the Obstetrical department of Municipal Hospital No 1, Chisinau, the Republic of Moldova. Methods of data collection in the study were based on extraction of medical documentation data from archive to complete the elaborated questionnaire for research. Statistical processing was performed using the program "Microsoft Office Excel 2010".

Results and discussion

From these 728 cases, 50 histories of low birth weight fetuses (<2500g) were analyzed in detail. The average weight of neonates was 2057 g. 27 fetuses (54%) were diagnosed as intrauterine growth restricted fetuses. RGOG Green-top guideline defines small–for–gestational age as an infant born with a birth weight less than the 10th centile. For these standards or personalized population centiles are used [17]. The smaller is the percentile weight of the fetus the higher is the probability to have a growth restriction. Untrauterine growth restriction is not synonymous with small for gestation. 50–70% of small–for–gestational age fetuses are constitutionally small, others "pathologically small" or growth restricted. Such infants were shown to be at increased risk for neonatal death [18, 19]. For example, the neonatal mortality rate of small for gestational age infants born at 38 weeks was 1 percent compared with 0.2 percent in those with appropriate birthweights [20].

The average weight of fetuses with the diagnosis of intrauterine growth restriction was 1989 g. 18.52% of infants had a very low birth weight (1000-1499 g). 84.48% of infants had low birth weight (2500-1500 g). In our study we did not have infants with extremely low birth weight (500-999 g).

Correct establishment of gestational age and determination of maternal risk factors improve the identification of small for gestational age with possible adverse pregnancy outcomes such as stillbirth, neonatal death, or low Apgar score [21, 22].

Risk factors as: maternal age, parity, maternal body mass index, mass weight gain during pregnancy, practice of exercise, diet, drug abuse, smoking, pregnancy interval, previous still-birth and pregnancy hypertension, diabetes, renal disease, antiphospholipidic syndrome, sex of the fetus, and complications of present pregnancy were included in the study protocol [23, 24].

The average age of mothers of children with IUGR was 29.07 years, the age ranged from 21 to 38 years. They were divided into 4 age groups: 21-25 years, 26-30 years, 31-35 and > 36 years. The majority of mothers belonged to the age group of 26-30 years (37.04%), 21-25 years old was 25.93%, 31-35 – 22.22% and> 36 years – 14.81%. It was found that the majority of mothers of children with IUGR were from the age group up to 30 years – 62.96%. Over 30 years were 37.04%. These mothers were also divided into 2 groups according to their social status: a housewife or a working woman. The group of housewives predominated: 56% versus 44% of employees. Parity of pregnancy of mothers ranged from 1 to 5. Mothers with the first pregnancy – 55.56%. The second pregnancy accounted for 29.63% of mothers, the third one - 7.41%, the fourth and fifth – 3.70%. By parity of birth, the mothers were divided into 3 groups: mothers with first birth made up the majority – 41.46%, second-birth – 29.27% and third birth were in 29.27%. Each of the examined risk factor has a likelihood ratio which can be used in calculation of general risk and particular antenatal management. This can include maternal serum markers in the first trimester of pregnancy, assessment of uterine Doppler, evaluation of the placenta morphology and serial ultrasound scans [25, 26].

Pregnancy-induced hypertension was diagnosed in 18.52%. Bad obstetric history was in 33.33% of pregnant women, 44.44% had scars on the uterus, 33.33% had miscarriage and 22.22% – infertility.

Gestational age was calculated using information from date of birth and estimated date of delivery determined in early pregnancy. The gestational age of children with IUGR was between 28 and 39 weeks. 28-32 weeks was 12.72%, 33-36 weeks – 43.80%, 37-39 weeks – 43.48%.

Normal fetal growth and development can be divided into three physiologic stages: cell replication and proliferation; cell migration and aggregation to form tissue and rudimentary organs; and increase in cell size and formation of functional organ structures. Thus in early pregnancy, very high mitotic activity is paired with very little change in mass, while in late pregnancy mitosis slows with a coincident rapid gain in weight [27]. As a result, genetic factors most influence fetal growth during the first half of pregnancy, and hormonal or environmental factors dominate later in pregnancy. Depending on this we can distinguish 2 different forms of intrauterine growth restriction: early and late [28]. These two forms are distinct by the cause, evolution, ultrasound parameters modifications, and postnatal outcome [29]. The diagnosis of intrauterine growth restriction in our study was mainly based on abdominal circumference value, with the prevalence of cases with 10th percentile abdominal circumference or linear growth chart. So the 10th percentile was used as a cut-off for hospitalization decision and fetal close monitoring [30].

The results of these ultrasound data (head circumference, abdominal circumference, femur length) were processed and compared to the percentile corridors: <3, 3-5, 5-10, >10. The difference between the estimated weight and the actual weight of the fetus was from 10 grams to 520 grams. The average difference was 255.71 grams. The difference <300 grams was 47.62%, > 300 grams was 52.38%.

The value of the head circumference of the fetuses in the majority was below the 10th percentile – 76.19%, head circumference >10 percentile – 23.81%, 5-10 percentiles – 9.52%, 3-5 percentiles – 33.33% and <3 percentiles were 33.33%. By the femur length most of the fetuses were found in the percentile > 10 (71.43%), 3-5 and 5-10 percentiles at 4.76% and in the percentile <3 were 19.05% of the fetuses. By the abdominal circumference most fetuses also belonged in corridor – the percentile 10 (52.38%), 3-5 and 5-10 percentiles at 4.76%, and <3 percentile – 38.10% (fig. 3). It was calculated for how many weeks the fetuses are lagging by the circumference of the abdomen from gestational age. Lagging by <2 weeks were 28.57%, for 2-4 weeks – 52.38%, for> 4 weeks – 19.05%. Fetal observation was based on fetal Doppler, amniotic fluid volume and cardiotocography [31, 32]. Of all the ultrasound results processed, 38.09% had pathological ombilical and middle cerebral artery Doppler (pulsativity index, resistance index and systolic/diastolic index). We used a Doppler follow-up program to distinguish various causes of small fetuses for gestational age. Small fetuses of small mothers and those small due to chromosomal aberration usually have normal Doppler tracings of umbilical and uterine arteries. The use of umbilical artery Doppler ultrasound has led to reductions in perinatal death related to complications of placental insufficiency and iatrogenic preterm delivery [33].

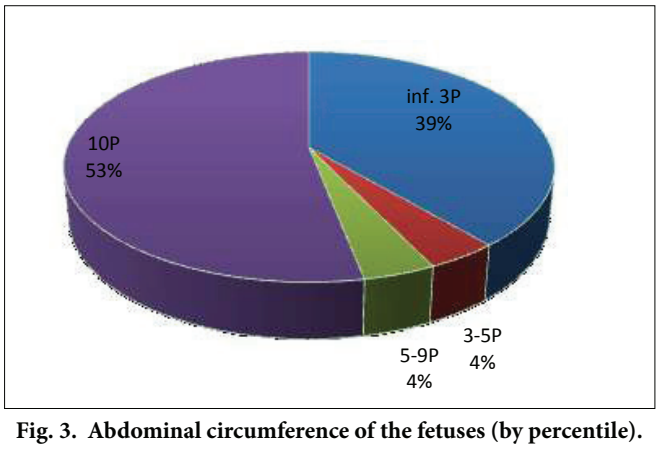

Fig. 3. Abdominal circumference of the fetuses (by percentile).

However, umbilical artery Doppler is not reliable for the identification of late-onset growth restriction and associated complications. Unfortunately, late-onset fetal growth restriction is more prevalent than growth restriction of early onset, and most adverse outcomes attributable to late-onset growth restriction occur in fetuses with normal umbilical artery Doppler waveforms [34].

Data of the circulation insufficiency, as data of blood circulation in the middle cerebral artery were in 38.09%. Of these, circulatory insufficiency was in 87.50% of cases. Most often there was a deficiency of I degree: 62.5% (IA-37.5%, IB – 25%). II degree of insufficiency – 12.5%, III degree – also 12.5%. Location of placenta was in 66.67% of cases anterior, 33.33% – posterior.

According to the delivery, 62.96% had a cesarean section, 37.04% had vaginal birth (fig. 4).

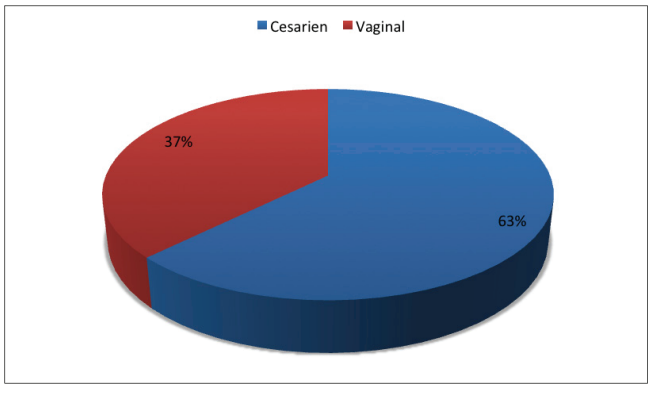

Fig. 4. Delivery modality of the fetuses.

As reported by Perroten et al., and Yogev et al. at least one half of all infants born with intrauterine growth restricted will experience intrapartum asphyxia at birth [35, 36]. Meconium aspiration and fetal hypoxia are also common [37]. Guidelines suggest that C-sections are more appropriate for infants with intrauterine growth restriction due to these risk factors and as mentioned earlier, due to their small size [14-16].

The female sex of newborns prevailed: 59.26%, male – 40.74%. We were also interested in Apgar score of the neonates, as in literature the antenatal detection and monitoring program for fetuses suspected with intrauterine growth restriction result in a better neonatal score, compared with cases of fetuses not identified antepartum [38].

The Apgar score at 1st minute for newborns with IUGR varied from 4 to 8. More children had score 7 (59.26%). Score 8 received 14.81% of infants, 4 – 3.70%, 5 and 6 points for 11.11% of newborns. The Apgar score at 5th minute – 7 points received 55.56% of children, 8 points – 33.33%, 5 points – 3.7%, 6 points – 7.41%.

Conclusions

The diagnosis and the management of intrauterine growth restriction still constitute a clinical dilemma. The prevalent criteria for diagnosis of intrauterine growth restriction in our study were foetal abdominal circumference below 10th percentile (52.3 %). The ultrasound evaluation showed to have an average sensitivity in the predicting the foetal weight at birth (47.6%). In the majority of cases the delivery was done by cesarian section (62.9 %), with the most frequent indication for foetal extraction – vascular redistribution and beginning of cerebral vasodilatation (37.5 %). Accurate diagnosis of intrauterine growth restriction can be achieved by improvement of methods for assessing the foetal biometry.

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Usage of cardiotonic drugs at the intensive care units

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Abstract

Background: Circulation insufficiency is one of the most common dysfunctions in the patients admitted to the intensive care units (ICU) [1]. These patients need an intravenous (IV) vasoactive drug administration to optimize or support cardiovascular system (CVS). Emergency situations, hard work conditions, difficult devices' usage and a lot of other specific factors of complex environment of ICU create favorable conditions for the occurrence of medical errors (ME).

Material and methods: Within this prospective study were examined the methods of administration and the types of the errors that were found during the administration of the following drugs: epinephrine, noradrenaline, dopamine and dobuthamine. In the period of time May – September 2016, were examined 50 patients from ICUs from 4 different hospitals. The age limits were between 31-100 years old. The data collection was accomplished on the base of a questionnaire prepared beforehand.

Results: From all the number of examined patients, 33 (66%) were men and 17 (34%) – women. The body weight was indicated in the medical notes of 21 (42%) patients. To 15 (30%) of them was administrated the adrenaline, noradrenaline had the incidence in 15 patients (30%) and dopamine – 17 patients (34%).

Conclusions: Tracked dosage errors in 20% of cases, 4% of them were found at dilution administration of the drugs. The inscription of administered drug in medical notes was lacking in 2 uses.

Key words: cardiotonic medication, medication error, automatic syringe pump, dilution.

Introduction

Circulatory failure is one of the most common disorders in patients admitted to the intensive care units (ICU) [1]. These patients often need intravenous (IV) vasoactive drug administration to optimize or support the function of cardiovascular system (CVS).

Cardiac output together with the blood elements ensure the fundamental necessity of the tissues, that is adequate transport of oxygen to maintain their functionality. Sequelae or their functional decompensation may occur in vital organs with limited capacity to compensate the hypotensive flares (brain, heart, kidneys, etc.). Blood pressure (BP) management is one of the main tasks of intensivist physicians and a number of actions are used for this purpose. Removing of cause (eg. hemorrhage, combustion treatment etc.) is the first task which most often is done in teams with specialists in other fields. Another vital intervention is the fluid-responsiveness, which is performed with crystalloid solutions (sol. of NaCl 0.9%, Ringer's sol., etc.) or colloids (prepared from starch, gelatin, etc.). If the infusion therapy is inefficient and the cardiac output does not ensure the needs of tissues, cardiac drugs are chosen.

Cardioverter and vasoconstrictor preparations are frequently used in the ICU and resuscitation department in order to maintain a working blood pressure and satisfactory cardiac output in patients.

It is extremely important to dose those preparations with vigilance in critically ill patients, who typically have more concomitant diseases. Taking into account that the doses are expressed in mc/kg/min., they are extremely small, and serious or even lethal side effects may occur even in case of a minor dosage error. Emergency situations, the harsh working conditions, the use of sophisticated equipment and many other factors specific to the complex environment of the ICU create a favorable ground for medication errors (ME).

Health care system is not infallible. Errors are common in most of the health care system and are reported as the seventh most common cause of death [2].

In the ICU, on average, 1.7 errors per day refer to a patient [3] and all have a life-threatening potential. Medication errors represent 78% of serious medical errors in the ICU [4]. The most common ME have been identified at the nurse level, which is 19% of all adverse events and representing more than 7,000 deaths annually in the USA [5].

Besides that the patient's safety is endangered. It should be noted that ME, which have not resulted in death, but caused damages, required additional drug administration. Respectively, it increases directly or indirectly the cost and length of hospitalization. Epiphenomenally, the risk of other ME occurrence increases. Although not all ME result in damage and often remain unnoticed.

Material and methods

The method of administration and the types of errors we encountered during the administration of the following preparations: epinephrine, noradrenaline (norepinephrine), dopamine and dobutamine were researched during this prospective study.

Epinephrine, delivery form: adrenaline hydrotartat, 0.18% solution for injection in 1 ml ampoules. Indications: cardiac arrest, status asmaticus, heart failure, shock. Dose: 2 mcg/min bronchodilator effect, 2-10 mcg/min inotropic effect, more than 10 mcg/min vasopressor effect. Side effects: hypertension, tachycardia, arrhythmias, skin necrosis in case of perivenous administration, vasoconstriction on splanchnic vessels. Noradrenalin is a 0.2% solution for injection in 1 ml

Table 1

Indications according to the diagnosis

	Adrenaline	Noradrenaline	Dopamine	Dobutamine	Adrenaline +Dopamine	Noradrenaline + Dopamine
Sepsis (septic shock)	1	7	2	-	-	-
Massive surgeries	4	5	8	-	1	-
Massive injuries	7	1	4	-	-	1
Cardiogenic shock (heart failure)	1	2	3	-	-	1
Hemorrhages	2	-	-	-	-	-
Total	15	15	17	-	1	2

ampoules. By the chemical structure, it distinguishes from adrenaline by the lack of methyl group to the nitrogen atom of the amino group of the side chain. Indications: hypotensive states (sepsis, shock) mainly due to its predominant vasoconstrictor effect. Dose: 1-30 mcg/min produces vasoconstriction without significant change in cardiac output and heart rate. Side effects: bradycardia, arrhythmia, anxiety, headache, hypertension, necrosis in case of perivenous injection. Dopamine is a 4 mg solution for injection in 5 ml ampoules. Indications: heart failure, shock conditions (except hypovolemic shock). Dose: 2-10 mcg/kg/min inotropic action prevails, 10-20 mcg/kg/min vasopressor effect prevails. Side effects: hypertension, tachycardia, arrhythmias, skin necrosis in case of perivenous administration, vasoconstriction on splanchnic vessels. Dobutamine is a 0.5% solution for injections in 50 ml ampoules and 1.25% in 20 ml ampoules; freeze-dried powder for injection solutions in 0.25 and 0.53 g. By the chemical structure, it is a dopamine catecholamine and differs from dopamine by the fact that a hydrogen atom of the amino group is replaced by paraoxyphenylmethylpropyl radical. Indications: heart failure, inotropic effect, increasing the heart rate to a lesser extent than dopamine, decreases the ventricular filling pressure, it is preferred in the treatment of decompensated heart failure. The peripheral vascular resistance remains unchanged or falls slightly. Dose: 5-20 mcg/kg/min. Side effects: arrhythmias, hypertension, angina pectoris, phlebitis [6-7]. 50 patients were collected from the ICU, in the period May-September, 2016. The lower age limit was 31 years and the upper one – 100 years. Data collection from patients was based on a questionnaire drawn up in advance.

Results and discussion

From all the number of examined patients, 33 (66%) were men and 17 (34%) were women.

The body weight was indicated in the medical card of 21 (42%) patients. This fact indicates a potential medication error. This problem is caused by poor equipment in triage points, on the one hand, or by beds in specialized departments that are old and scales are not fitted in their construction.

Age limits were between 31-100 years.

According to the obtained results, we can see that the dose in patients, whose body weight was not indicated, was calculated empirically by the doctor. But most often the dose was corrected depending on changes in BP.

Cardiotonic medication was indicated in the following diagnoses: sepsis (or septic shock), massive surgeries, cardiogenic shock (heart failure), massive injuries and hemorrhages (tab. 1).

Statistical analysis of data

From the total number of patients, the adrenaline was administrated in 15 (30%) of them. In 9 (18%) of cases was indicated the amount of solute in the medical cards and in 6 (12%) of the cases was noted the dose. The way of administration was represented by 9 (18%) of the cases of administration by dilution and 6 (12%) of the cases of administration by automatic syringe pump. The recording of medication in the medical card did not correspond to the way of administration. Dosage errors were detected in three cases, two of which were administered by automatic syringe pump.

The administration of noradrenaline had an incidence in 15 patients (30%). The dose administration was noted in the medical card in 14 patients (28%). Of these, only one case (2%) represented the way of administration by dilution. Dosage error was attested in two cases. The drug administration was not indicated in the medical card in one patient.

The subjects who received permanent medication of dopamine represented a group of 17 patients (34%) and in 5 patients (10%) of these was noted the substance quantity in the volume of injection and in 12 patients (24%) was noted the dose of administration. The way of administration was dominated by the automatic syringe pump – 13 cases (26%). Dosage error was proven in five cases.

3 patients (6%) received combined medication, of which 2 patients were administered noradrenaline associated with dopamine, and one patient was administered adrenaline associated with dopamine. The dose of administration was noted in the medical cards in patients who received the combined medication (6%) of cardiotonic (tab. 2).

Unfortunately, we have not encountered patients receiving dobutamine during the study.

Variations in blood pressure (BP) and heart rate (HR) were

The Moldovan Medical Journal, April 2017, Vol. 60, No 2

Table 2

Recording of drug in the medical card and administration type

	Adrenaline	Noradrenaline	Dopamine	Dobutamine	Adrenaline +Dopamine	Noradrenaline + Dopamine
Substance quantity	9	1	5	-	-	-
Dose (mcg/kg/min.)	6	14	12	-	1	2
Administration by dilution	9	1	4	-	-	-
Administration automatic syringe pump	6	14	13	-	1	2
Dose error	3	2	5	-	-	-

indicated in the medical card at a rate of 100%. This shows that these two values serve as landmarks at the administration of cardiotonics in emergency cases. This fact explains the incidence of cases when the drug administration (2%) was not noted in the medical card or the incorrect dose recording during the data collection (20%).

The nurse knows only the amount of solute and the infusion in proportion of 98%. This can be a source of errors even if the doctor performed correctly all procedure maneuvers.

Cardiotonic drugs were administered through the central catheter in a proportion of 98%, most often simultaneously with the secondary solution.

A label written by hand was attached in the absolute majority of studied cases, and the type of drug and quantity of administered substance were indicated on it.

A medical error becomes a medication incident only when the patient is harmed. Not all the incidents connected with the medication are caused by the medication errors. In an analysis of the 2000 anesthetic incidents, 7.2% were caused by the medication errors and not one of them was fatal [8].

Incorrect written prescription represents a frequent cause of medication errors. At a University hospital, from all the amount of the errors, 57% of them were mistakes or lapses, 39% - were the errors, caused by unconscious deviation from the rules and only 4% were conscious deviations from the rules. None of the involved staff could explain what had happened, although the main causes are: hurry, tiredness, interruption by somebody else, insufficient knowledge of the specific medication, confusion while watching another patient. Inexperienced doctors and unsupervised residents have the predisposition to make the clinical errors [9].

Medication transcription or some numeral dates are susceptible to errors. Doctors sometimes transcribe medication records. The error rate of the transcription is approximately 1%, but a third part of them could be fatal. The usage of computer systems in medical indications reduces this risk [10].

Dosage and incorrect rates, including unintentional bolus administration, are frequent errors found in intervenous administration [11].

Medication errors represent an important cause of patients' morbidity and mortality. Therefore, only 10% of the errors represent the RA and have severe consequences for the patients. The Institute of Medicines' rate from USA has shown that from 44 000 to 98 000 patients die annually as a consequence of ME and a significant part is caused by the drugs [12].

In ICUs the majority of the drugs are administered in perfusions based on the weight of the patient. Weight estimation and the dose calculation by math's searching increase the risk of the ME apparition. Because of that for the drug administration are often used difficult devices, but devices' defects could lead to drug administration with the wrong speed. We must be aware of the fact that the administration with the inappropriate speed such drugs as cardiotonics and anticoagulants can lead to some consequences with the lethal end [13].

Financial costs of adverse events, speaking about the additional treatment and additional hospitalization period, are considerable. One of the most consistent findings of reviews of registration is that, in average, a patient suffering an adverse event stays an additional six to eight days in the hospital. When the prices are established and the findings are extrapolated at the national level, the prices are reasonable.

Nurses play a very important role in patients' security, because these are the providers of the medical system, whom the patients spend the majority of time with. This fact has important implications. In case of decreasing the rate of nurse-patient, the staff rates could be associated with a high risk level of medical errors, the rates of 1:1 or 1: 2 seem to be the safest in ICU [14].

Strategies of the prevention

Incident Reporting System supports the necessity of an organizational commitment to improve general patient's safety, including the medication errors. The studies have discovered that the safety climate in a unit could predict the incidence of the ME. A more positive culture is associated with fewer errors [15].

The mechanisms suggested for the improvement of the results are various. The fear of adverse consequences can be major obstacle to the accurate reporting of errors, from 50% to 96% of them are unreported [16].

The usage of checklists is well-spread not only in ICUs, but at Emergency medicine, as well. The steadiness is caused by the low cost of the usage, easiness and high efficiency. Check-

lists have the role of the direction of the doctors for the successful actions that need quick and productive decisions in critical situations. Respectively is omitted a part of the ME that could be caused by the situations associated with a high stress rate.

The system of medical prescriptions is computerized. This system has the role to help and inform the doctor about the possible adverse reactions using the data base of the patient. In this base are available the results of all the investigations and medication got from the hospitalization.

Computer System presents all the general steps of the prescription and transcription of the drug [17].

The System of administration through a bar cod (SABC) is a system of the bar codes built to prevent ME and to improve the quality and safety of drug administration. General objectives of the SABC are to improve accuracy, prevent errors and generate online medication administration. It consists of Bar-Code reader, a portable computer or an office PC, a server and software. When a nurse is administrating a drug to a patient, she could scan the code from the breastplate of the patient and from the package of the drug. The appropriate software could check it and then, if it is the corresponding patient, the corresponding drug at the appropriate dosage at appropriate moment by the appropriate way is administered ("Five rights") [18]. SABC was created as an additional control to help the nurse at drug administration. At the same time, it can not replace the experience and professional judgment of the nurse.

The usage of intelligent pumps, that were evaluated, has shown the incidence rate of ME was 4% less than the pumps of the previous generations [19]. As well, there are used more types of procedures to optimize the rate of the perfusions, using the same syringe or 2 syringes with or without the period of superposition [20].

Conclusions

1. As a result of analysis of the above data, dosage errors have been ascertained in proportion of 20%, of which 4% of errors were encountered at the drug administration by dilution. The drug administration was not registered in the medical card in one case.

2. The exact body weight is known exactly in 21 patients (42%), which suggests that the medical personnel is facing limited technical opportunities.

3. The recommended doses for cardiotonic drugs investigated in this study have an orientation character. From the beginning of administration till the establishment of constant infusion speed, the dose undergoes many changes until it reaches the reference values of BP.

4. Mean arterial pressure and heart rate are the key indicators starting with the initiation of medication and subsequent continuous monitoring of patients. ECG also has an important role during monitoring, particularly in cardiac patients.

5. The incidence of four cases of dose errors in patients receiving cardiotonic drugs by the automatic syringe pump indicates that the use of modern equipment, not only does not limit the incidence of ME, but it may be even a source.

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REVIEW ARTICLES

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The role of homocysteine in endothelial dysfunction

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Abstract

Background: Homocysteine is a sulfur-containing intermediate product in the normal metabolism of methionine, an essential amino acid. Hyperhomocysteinemia defines the state in which concentrations of homocysteine exceeds normal level. Homocysteine is located at a metabolic branch point and can either be irreversibly degraded to cysteine via the transsulfuration pathway, or conserved by remethylation back to methionine. Folic acid, vitamin B_{12}, and vitamin B_6 deficiencies and reduced enzyme activities inhibit the breakdown of homocysteine, thus increasing the concentration of intracellular homocysteine. Being cytotoxic, homocysteine is increasingly exported from the cell to become detectable in plasma. In recent years the amino acid homocysteine has achieved the status of an important factor in vascular disease, diseases of aging, and other fundamental processes in biology and medicine. Hyperhomocysteinemia may alter vascular morphology, stimulate inflammation, activate the endothelium and the blood clotting cascade, and inhibit fibrinolysis. As a result, hyperhomocysteinemia is associated with loss of endothelial antithrombotic function and induction of a procoagulant environment. The role of homocysteine in endothelial dysfunction is thought to be mediated by mechanisms including oxidative stress. Vascular injury could be caused by an imbalance between nitric oxide production from dysfunctional endothelial cells and homocysteine concentrations.
Conclusions: Hyperhomocysteinemia is associated with alterations in vascular morphology, loss of endothelial antithrombotic function, and induction of a procoagulant environment.

Key words: homocysteine, endothelial dysfunction, hyperhomocysteinemia, endothelium, oxidative stress.

Introduction

In recent years the amino acid homocysteine has achieved the status of an important factor in vascular disease, diseases of aging, and other fundamental processes in biology and medicine [25]. After its discovery in 1932, homocysteine was characterized as an important intermediate in methionine metabolism. Little was known about its biomedical significance until 1962, when children with mental retardation, accelerated growth, and propensity to thrombosis of arteries and veins were found to excrete homocysteine in the urine [19,25]. The cause of homocystinuria in most of these cases is deficiency of the enzyme cystathionine synthase, a pyridoxal phosphate-dependent enzyme [25]. In 1968, a second case of homocystinuria caused by deficiency of a different enzyme, methionine synthase, a folate and vitamin B12–dependent enzyme, was critical in the discovery of the atherogenic potential of homocysteine [25]. McCully and Wilson proposed the "homocysteine theory of artheriosclerosis" in 1975 on the basis of pathological examinations of autopsy material from children with homocystinuria [20]. However, only within the past 5 years has homocysteine taken its place among other major risk factors such as cholesterol, smoking, and obesity [20]. Homocysteine is now widely accepted as a major independent risk factor for cardiovascular, cerebrovascular, and peripheral vascular disease [13,17,20,33]. However, the precise mechanisms underlying this association, although intensively studied, are still incompletely solved [30].

Homocysteine metabolism

Homocysteine is located at a metabolic branch point and can either be irreversibly degraded to cysteine via the transsulfuration pathway, or conserved by remethylation back to methionine (fig. 1) [12,30].

First, methionine is activated by the enzyme methionine adenosyltransferase (MAT) and ATP to form S-adenosylmethionine (SAM) [30]. SAM is the primary methyl group donor for many vital biological processes, including methylation of DNA, RNA, proteins, lipids and neurotransmitters [10,11,13,16,28,29,30,31,32,33,345]. Upon transmethylation, SAM is converted to S-adenosylhomocysteine (SAH), which is further hydrolyzed by the enzyme adenosylhomocysteine hydrolase (SAHH) to homocysteine and adenosine. This reaction is reversible and favors SAH synthesis [12,30].

The transsulfuration pathway, mainly limited to liver and kidneys, is initiated with the condensation of homocysteine and serine to form cystathionine, in a reaction catalyzed by the enzyme cystathionine β-synthase (CBS), with pyridoxal phosphate (vitamin B6) as co-factor [12,13,30,31,34]. Cystathionine is further metabolized to produce cysteine by another enzyme – cystathionine γ-lyase (CGL). Besides protein synthesis, cysteine is used in the synthesis of glutathione, an important cellular antioxidant also involved in detoxification of many xenobiotics [30].

In remethylation, homocysteine acquires a methyl group from 5-methyltetrahydrofolate (5-MTHF) or from betaine

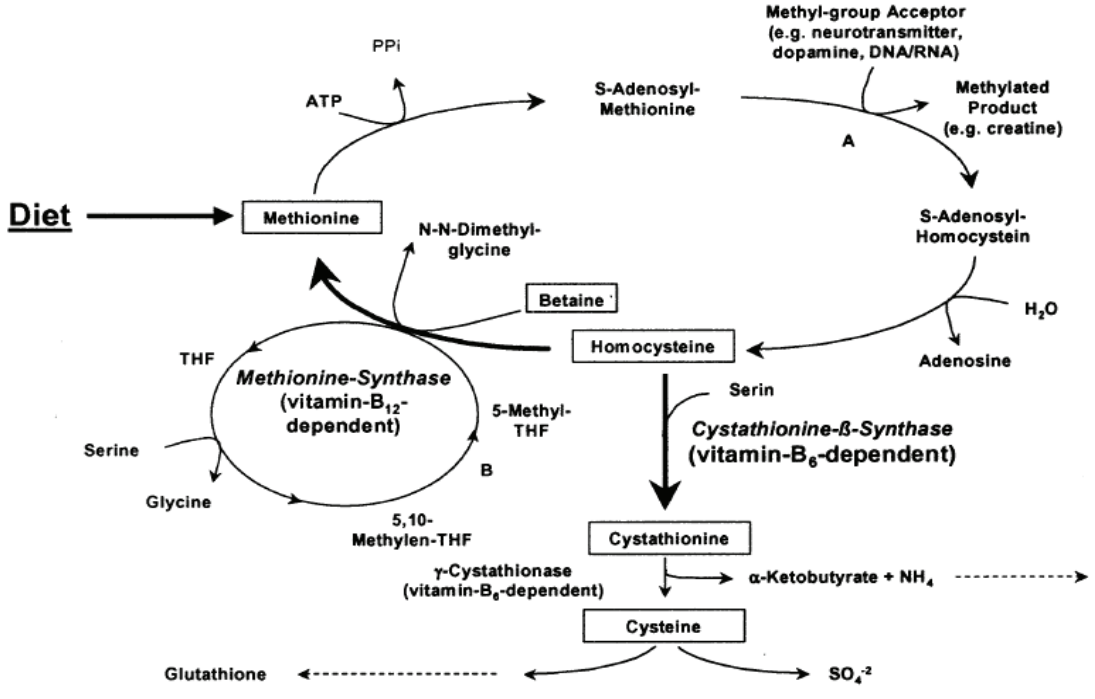

Fig. 1. Homocysteine metabolism (A – enzyme methionine adenosyltransferase, B – enzyme 5,10-methylenetetrahydrofolate reductase) [33].

to form methionine. The reaction with MTHF occurs in all tissues and is vitamin B_{12}-dependent, while the reaction with betaine is confined mainly to the liver and is vitamin B_{12}-independent [31].

Homocysteine remethylation occurs by receiving the methyl group from 5-MTHF, which links the folate cycle with the homocysteine metabolism (fig. 1). 5-MTHF is the active folate derivative and the main circulating form of folate in plasma. It is produced from 5,10-methylenetetrahydrofolate (5,10-MTHF) by the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which uses flavine adenine dinucleotide (FAD – the active form of vitamin B_2) as co-factor [1,4,33,34]. The methyl group from 5-MeTHF is transferred via vitamin B_{12} to homocysteine, in a reaction catalyzed by the enzyme methionine synthase (MTR), with production of tetrahydrofolate (THF) [27,30,33,34]. THF is then recycled to 5,10-MTHF in the presence of serine and vitamin B_6 by the enzyme serine hydroxymethyltransferase (SHMT) [30].

Over time, the cobalamin (I) cofactor of MTR is oxidized to form cobalamin (II), leading to inactivation of MTR. Thus, the enzyme methionine synthase reductase (MTRR) is required for reversion of oxidized cobalamin (II) to CH_3-cobalamin (III) to maintain the activity of MTR [22]. The folate-dependent remethylation pathway is present in nearly all cells, except red blood cells [34].

Alternatively, in liver and kidney, methyl groups can also be donated by betaine (also known as trimethylglycine, an intermediate of choline oxidation), in a reaction catalyzed by the enzyme betaine-homocysteine methyltransferase (BHMT) [30].

The intracellular concentration of homocysteine is under tight control. Once formed in the cell, homocysteine is quickly either metabolized to cysteine or remethylated to methionine. In addition, if one of these pathways is compromised, leading to higher intracellular production than elimination, the excess of homocysteine is rapidly exported to the blood. Hence, cellular export of homocysteine reflects the balance between homocysteine production and catabolism. [12,30].

SAM plays a central role in the regulation of homocysteine metabolism, by coordinating the fate of homocysteine towards remethylation or transsulfuration pathways; it is an allosteric inhibitor of MTHFR and an activator of CBS activity. When the levels of SAM are adequate to sustain methylation demand, the partitioning of homocysteine between both metabolic pathways is approximately equal. In case of excess of methionine supply, an increase in tissue SAM levels occurs, and homocysteine degradation to cysteine is favored. Moreover, SAM also regulates homocysteine remethylation through inhibition of BHMT activity. Conversely, if methionine levels are low, for example during fasting, low SAM levels will neither activate CBS nor inhibit MTHFR, resulting in conservation of homocysteine via remethylation back to methionine [12,16,30,31].

Folic acid, vitamin B_{12}, and vitamin B_6 deficiencies and reduced enzyme activities inhibit the breakdown of homocysteine, thus increasing the concentration of intracellular homocysteine [29,33]. Being cytotoxic, homocysteine is increasingly exported from the cell to become detectable in plasma [33].

Causes of hyperhomocysteinemia

Hyperhomocysteinemia is a terminology suggested to describe the presence of abnormal elevation in total plasma homocysteine levels. In the fasting state, normal plasma levels

of homocysteine are less than 12 μmol/l [1,2,5,6,9,14,21,30]. Pregnant women have lower plasma tHcy than nonpregnant women. The mean tHcy concentration in pregnant women is 5–6 μmol/L, and tHcy concentrations >10 μmol/L are rarely observed [28].

Table 1

Determinants of plasma tHcy [28]

Causes	Effect
Genetic factors	
Homocystinuria	↑↑↑
Heterozygosity for CBS defects	↑
Down syndrome	↓
MTHFR 677C→T (homozygosity)	↑
Other polymorphisms	↑
Physiologic determinants	
Increasing age	↑
Male sex	↑
Pregnancy	↓
Postmenopausal state	↑
Renal function, reduced glomerular filtration rate	↑
Increasing muscle mass	↑
Lifestyle determinants	
Vitamin intake (folate, B_{12}, B_6, B_2)	↓
Smoking	↑
Coffee	↑
Ethanol intake	↑
Lack of exercise	↑
Clinical conditions	
Folate deficiency	↑↑
Cobalamin deficiency	↑↑↑
Vitamin B6 deficiency	↑
Renal failure	↑↑
Hyperproliferative disorders	↑
Hypothyroidism	↑
Hyperthyroidism	↓
Early stage of diabetes	↓
Late stage of diabetes	↑
Drugs	
Folate antagonists (Methotrexate, Trimethoprim, Anticonvulsants, Cholestyramine)	↑
Cobalamin antagonists (Nitrous oxide, Nitric oxide, Metformin, H2-receptor antagonists, Omeprazole)	↑
Vitamin B6 antagonists	↑
Sulfhydryl compounds	↓
Estrogens, Tamoxifen	↓
Androgens	↑
Cyclosporin A, Diuretics, Fibrates	↑

↓ – decrease in tHcy, ↑ – moderate hyperhomocysteinemia (12 – 30 μmol/l), ↑↑ – intermediate hyperhomocysteinemia (30 – 100 μmol/l), ↑↑↑ – severe hyperhomocysteinemia (>100 μmol/l)

Determinants of plasma total homocysteine (tHcy) include genetic, physiologic, and lifestyle factors; various diseases and drugs (tab. 1) [9,17,28,33,34]. The causes of increased tHcy concentrations vary according to the age of the person and the degree of tHcy increase [20,27,28,33]. Low folate or cobalamin status or renal impairment account for the majority of cases with increased tHcy [3,11,31,32,33]. In populations eating food fortified with folic acid, renal impairment and cobalamin deficiency are the most important determinants. Homozygosity for the MTHFR 677C→T polymorphism is the most common genetic determinant. Individuals with the MTHFR 677TT genotype usually have higher tHcy than those with the 677CC variant, but it depends on the folate status. Most other genetic polymorphisms in enzymes related to homocysteine have little effect on tHcy concentrations [28,29].

Circulating species of homocysteine in plasma

Homocysteine is present in plasma in various forms in different proportions [20,27,33]. Human plasma contains both reduced and oxidized species of homocysteine [20]. The concentration of free homocysteine in plasma is very low and accounts for less than 2% of total plasma homocysteine in normal subjects [27,33] and the oxidized forms of homocysteine usually comprise 98–99% of total plasma homocysteine in human plasma [20]. Disulfide forms also exist with cysteine and with proteins containing reactive cysteine residues (protein-bound homocysteine). The latter oxidized forms are referred to as mixed disulfides. The concentration of homocystine and homocysteine-cysteine represents approximately 10-15%, and protein-bound homocysteine accounts for over 80% of the measured total homocysteine in normal plasma [27]. Total homocysteine, therefore, is the sum total of all forms of homocysteine that exist in plasma or serum [20]. Only minute amounts of homocysteine are found in the urine of healthy subjects. The term "homocystinuria" should therefore be reserved for inborn errors of metabolism characterized by extremely elevated plasma homocysteine levels and substantially increased excretion of homocysteine in the urine [33].

Mechanisms of homocysteine-mediated vascular damage

Hyperhomocysteinemia may alter vascular morphology, stimulate inflammation, activate the endothelium and the blood clotting cascade, and inhibit fibrinolysis [1,5,6,9,10,11,12,13,1418,33,34,35]. As a result, hyperhomocysteinemia is associated with loss of endothelial antithrombotic function and induction of a procoagulant environment. Most known forms of damage or injury are due to homocysteine-mediated oxidative stresses. Chief among these are changes in the intracellular redox potential, interference with the nitric oxide (NO) system, and activation of transcription factors with stimulation of gene expression [33].

Observations in clinical and animal studies have identified potential pathophysiological targets where homocysteine exerts its damaging effect. Those targets include endothelial cells (ECs), vascular smooth muscle cells (VSMCs), connective tissue, platelets, coagulation factors, lipids, and NO signal transduction molecules. Unfortunately, there is not an established, unifying hypothesis by which homocysteine evokes vascular damage. However, there are numerous biological and

biomolecular mechanisms that have been heavily studied and proposed to explain the pathological changes associated with elevated tHcy levels [34].

Oxidative stress is possibly the most detrimental stressor in the pathogenesis of most diseases. Studies have shown that the pro-oxidative homocysteine exerts direct biological damage to vascular cells and tissue through an oxidative mechanism that damages lipids, nucleic acids, and proteins [15,18,19,23,34]. An alternative hypothesis to that of a direct effect of reduced homocysteine on endothelial cell injury is that homocysteine is acting indirectly through its oxidation and the concomitant production of reactive oxygen species [7,24].

Under aerobic conditions (in the presence of molecular oxygen as an electron acceptor) and at physiological pH, thiols such as homocysteine, oxidize to form disulfides, according to the general reaction:

2 Homocysteine (RSH) + O_2→ Homocysteine (RSSR) + [O^-_2] → H_2O_2 [19,24]

In plasma, this reaction can be catalyzed by transition metals such as copper and cobalt. Homocysteine can autooxidize readily via general thiol oxidation mechanism described above and form homocystine, or oxidize other thiols such as cysteine and glutathione to form mixed disulfides, or oxidize free cysteine residues on proteins and peptides to form mixed disulfides [19]. Homocysteine itself has the ability to generate potent reactive oxygen species (ROS) when oxidized due to its highly reactive sulfhydryl group. In the circulation, this thiol undergoes rapid metal-catalyzed sulfhydryl auto-oxidation, leading to the generation of superoxide and hydrogen peroxide [15,19,20,27,34,35].

In addition to auto-oxidative ROS production, decreased homocysteine clearance and resultant accumulation further increases the production of harmful oxidants that collectively spurs on the negative cascade of vascular complications. Homocysteine has a detrimental effect on vascular cells and tissues as a result of oxidative damage to lipids, nucleic acids, and proteins. The injurious oxidative stress exerted by homocysteine relies either on auto-oxidation of the highly reactive thiol group of homocysteines or on the formation of intracellular superoxide and peroxyl radicals with concomitant inhibition of cellular antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase [13,34].

As a consequence of homocysteine-produced oxidative radicals, there is a critical impairment in the production of endothelium derived NO by several different mechanisms [34,35]. Homocysteine decreases the bioavailability of NO, one of the major endothelium-dependent vasodilators that is produced by the endothelial isoform of nitric oxide synthase (NOS). This effect is caused either by an accelerated oxidative inactivation of NO and/or eNOS or by an increase in serum aasymmetrical dimethylarginine (ADMA), an endogenous inhibitor of eNOS, thus decreasing NO production [13,34,35]. Also, studies have shown that homocysteine suppresses NO production without altering NOS protein levels or enzyme activity and the homocysteine-induced endothelial injury and subsequent reduction in NO production are primarily associated with increased ROS levels [34].

In the walls blood of vessels, NO contributes to the regulation of systemic blood flow and pressure by activating intracellular signaling pathways that modulate calcium levels in VSMC resulting in vasodilation. Homocysteine is known to decrease vascular function by the oxidative depletion of biologically active NO. Homocysteine has also been shown to cause striking changes in vessel wall structure by inducing extracellular matrix alterations that fragment the arterial internal and medial elastic lamina. Unlike the growth retardation of the endothelium, homocysteine has been associated with myointimal hyperplasia and VSMC hypertrophy [2,4,6,8,9,17,20,27,34,35]. It has been shown that homocysteine stimulates VSMC proliferation by the activity of homocysteine-generated oxygen radicals that activate cytokines that are active in the initial phase of the proliferative process. It has also been reported that the homocysteine-mediated reduction in NO synthesis and release by injured ECs causes the release of growth factors that provoke proliferation of nearby VSMC [34].

Homocysteine has been shown to induce vascular inflammation by enhancing the expression of pro-inflammatory cytokines, such as monocyte chemoattractant protein 1 (MCP-1), which regulates migration and activation of monocytes/macrophages, and interleukin 8 (IL-8), which is an important chemoattractant for neutrophils and T-lymphocytes [13]. Homocysteine has been shown to initiate the process by increasing the expression and plasma levels of the inflammatory cytokine, tumor necrosis factor alpha (TNF-α), and enhancing the activation of a redox-sensitive nuclear inflammatory transcription factor, nuclear factor-kappa B (NF_kB), in the vasculature [19,34,35].

It has long been believed that homocysteine may cause lipid peroxidiation by an oxidation-dependent pathway [2,4,34,35]. Homocysteine generates oxidative radicals that initiate oxidative degradation of lipids on the EC surface, which causes loss of membrane function and increased permeability. Clinical data have shown that patients with hyperhomocysteinemia have an increase in end products of lipid peroxidation such as F_2-isoprostanes and malondialdehyde [34].

A more recent concept concerns activation of the unfolded protein response (UPR) that is triggered when unfolded or misfolded proteins accumulate in the endoplasmic reticulum (ER). This ER stress induces the expression of several molecular chaperones and other stress response proteins, which are aimed at restoring correct protein folding or retranslocating defective proteins back to the cytosol for degradation in the proteasomes. In case of a prolonged ER stress, the UPR extends to the activation of apoptosis by various signaling pathways. This is precisely what happens in human endothelial cells after exposure to homocysteine in vitro: while inducing misfolding in the ER by altering the local redox potential and interfering with disulfide bond formation, homocysteine activates UPR and, subsequently, growth arrest and apoptosis (fig. 2) [13].

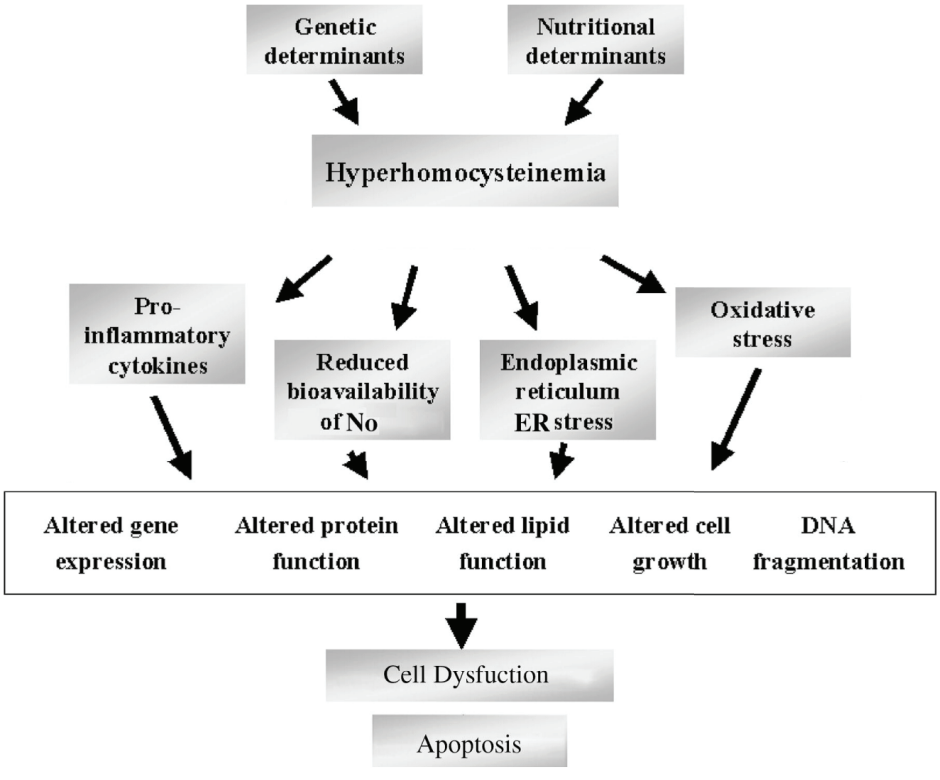

Fig. 2. Cellular and molecular mechanisms of hyperhomocysteinemia induced cell dysfunction [13].

These actions can be in connection with the widely believed capability of homocysteine to alter the surface properties of endothelial cells by changing their phenotype from anticoagulant to procoagulant [10,18,21,24,26].

Endothelial cells also possess several antithrombotic mechanisms to protect against intravascular thrombosis. However, elevated plasma homocysteine levels have been reported to cause an imbalance in coagulant and clotting properties toward a prothrombotic state in coronary and peripheral disease that is primarily mediated by the endothelial dysfunction [34].

In fact, physiological levels of homocysteine may enhance the binding of lipoprotein to fibrin. On the other hand, high levels of homocysteine reduce protein C activation, thus inhibiting its anticoagulant activity; induce a great inhibition, by more than 75%, of antithrombin III; inhibit the synthesis of anticoagulant heparan sulphate through an induced alteration of the redox potential; suppress thrombomodulin and inactivate its co-factor activity; block tissue plasminogen activator binding to endothelial cells; and activate tissue factor transcription [10,18,24,26].

Furthermore, it has been shown that homocysteine induces the activity of a protease which activates factor V, thus promoting coagulation even in the absence of thrombin. Homocysteine rapidly reacts with nitric oxide to form S-nitroso-homocysteine, which acts as a potent antiplatelet agent; the formation of this adduct may attenuate the production of peroxides from homocysteine, thus protecting against the atherogenic properties of homocysteine [10,18,19,24]. Vascular injury could be caused by an imbalance between nitric oxide production from dysfunctional endothelial cells and homocysteine concentrations [24,35].

Conclusions

This review focuses on disorders of homocysteine metabolism, on situations in which the metabolic mechanism is impaired and elucidates the mechanisms by which homocysteine can cause endothelial dysfunction. Thereby: (1) Homocysteine may increase oxidative stress; (2) Homocysteine may impair endothelial function and bioavailability of nitric oxide; (3) Homocysteine may impair vascular smooth muscle cell function; (4) Homocysteine may change extracellular matrix, collagen structure and function; (5) Homocysteine may induce a prothrombotic state; (6) Homocysteine may increase lipid peroxidation, and increase the oxidation of lowdensity lipoprotein; (7) Homocysteine may induce inflammation and apoptosis.

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Radiofrequency ablation – new insights into the modern treatment of atrial flutter and fibrillation

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Abstract

Background: Atrial fibrillation (AF) is associated with a 5-fold increase in the risk of stroke and a 3-fold increase in the incidence of heart failure. The increase in AF prevalence can be attributed both to better detection of silent AF, alongside increasing age and conditions predisposing to AF. Non-pharmacological measures aimed at «healing» AF were initially tested in open surgery. Searching for an approach with a greater chance of success led to the development of radiofrequency ablation (RFA). Only recently RFA technique began to be used extensively in people with AF, not being tested in large randomized studies, with establishment of remote results.

Conclusions: Catheter ablation is used successfully in patients suffering from symptomatic paroxysmal atrial fibrillation, as an alternative to drug therapy. Performed correctly by a trained and experienced electrophysiolologist, RFA allows us to get remarkable results, being possible suspension of treatment with antiarrhythmic drugs and to avoid its so well known side's effects. RFA with catheter is superior to antiarrhythmic drug therapy in preventing recurrence in both persistent AF and in the paroxysmal AF. The success rate of RFA in experienced centers for paroxysmal AF exceeds 70% a year. RFA reintervention is necessary in the approximately 9-20% of patients with more modest results. The frequency of major complications related to RFA is less than 5%. The restored sinus rhythm with RFA in patients with heart failure may be associated with significant improvement in left ventricular ejection fraction.

Key words: atrial fibrillation, radiofrequency ablation.

Introduction

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the most common sustained cardiac rhythm disorders and one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world [1]. In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries [2,3]. By 2030, 14–17 million AF patients are anticipated in the European Union, with 120 000–215 000 newly diagnosed patients per year [3,4,5].

The age of patients with this disease increases progressively, that currently the average age is between 75 and 85 years. This arrhythmia is associated with a 5-fold increase in the risk of stroke and a 3-fold increase in the incidence of heart failure. The increase in AF prevalence can be attributed both to better detection of silent AF, alongside increasing age and conditions predisposing to AF [1].

In many patients, AF progresses from short, infrequent episodes to longer and more frequent attacks. With time, many patients will develop permanent AF. In a small proportion of patients, AF will remain paroxysmal over several decades. Based on the presentation, duration, and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF. If patients suffer from both paroxysmal and persistent AF episodes, the more frequent type should be used for the diagnosis [1,6].

Patients who are primary diagnosed with AF are in the category called de novo AF. Many patients with AF are often asymptomatic and are diagnosed incidentally during a routine physical examination. If the patient has more episodes of AF lasting up to seven days and that stops on its own the category changes to paroxysmal AF. If AF lasting longer than 7 days is then known as persistent AF [7]. In this case to restore sinus rhythm it is recommended to perform planned electrical cardioversion. If the electrical cardioversion is ineffective, contraindicated or not performed and AF continues year or more the patient's AF is then known as permanent [8]. In addition to the above four AF categories, which are mainly defined by episode timing and termination, the ACC/AHA/ESC guidelines describe additional AF categories in terms of other characteristics of the patient [9].

Lone atrial fibrillation – the absence of clinical signs and symptoms or echocardiographic findings of rheumatic valve disease, ischemic heart disease, hypertension, pulmonary heart, cardiomyopathy thyrotoxicosis or the left atrium enlargement in patient under 60 years old.

Secondary AF – the occurrence of arrhythmias in certain situations or directly in the acute phase of diseases, such as during myocardial infarction, acute pericarditis, pulmonary embolism, infectious diseases, brain trauma or thoracic surgery [9].

AF is a chaotic atrial depolarization at a rate of 300-600 beats per minute and ventricular rate may vary depending on atrioventricular (AV) conduction. On the electrocardiogram (ECG) we have a completely irregular ventricular rhythm and fibrillatory waves of small amplitude and different morphology.

AF and atrial flutter (AFL) are two forms of supraven-

tricular tachyarrhythmia that in different periods of time can coexist on the same patient. Sources of rapid electrical discharges are automatic foci localized in the left atrium near the pulmonary veins or in a variety of other locations through both the left or right atrium [10].

AFL is atrial tachyarrhythmia with frequency of 250-350 beats per minute. AFL foci are often localized in the cavotricuspidian isthmus in the right atrium [10]. The prevalence of AFL is less than one tenth of the prevalence of AF. AFL often coexists with or precedes AF [1]. In typical, isthmus-dependent flutter, P waves will often show a "saw tooth" morphology, especially in the inferior leads (II, III, aVF). The ventricular rate can be variable (usual ratio of atrial to ventricular contraction 4:1 to 2:1, in rare cases 1:1) and macro-re-entrant tachycardias may be missed in stable 2:1 conduction [11].

Non-pharmacological measures aimed at "healing" AF were tested initially in open surgery. Searching for an approach with a greater chance of success led to the development of ablation with radiofrequency (RFA) without the need for open surgery, after having determined that, in many patients, AF is initiated and / or maintained by extrasystoles with the origin in the pulmonary veins. In the form of persistent AF, pulmonary vein isolation is not sufficient to achieve acceptable success rates but are often necessary to modify the atrial substrate (discrete ablation and / or linear ablation). Reintervention by RFA applies in the case of about 9-20% of patients. The frequency of major complications related to the ablation is less than 5%. Only recently RFA catheter technique began to be used extensively in people with AF, not being tested in large randomized studies, with the establishment of remote results. However, several well-conducted randomized trials and systematic reviews have shown that both in the persistent AF and paroxysmal AF, catheter ablation is superior to antiarrhythmic drug therapy in terms of preventing recurrences [12].

According to recent guidelines, prevention of recurrence of AF using RFA is warranted in patients with symptomatic paroxysmal form, RFA catheter may be considered after failure of first line antiarrhythmic drugs. Thus, in those without structural heart disease, RFA is an alternative to treatment by antiarrhythmic drugs if they have been found to be ineffective. In cases where the medication with amiodarone is the first line therapy due to the presence of contraindications for IC antiarrhythmic class RFA may be considered if amiodarone does not work [12]. The guides are equivocal regarding persistent AF patients. RFA can be indicated for cases of recurrent AF with severe symptoms after the failure of an antiarrhythmic drug. Such a recommendation is not based on solid evidence, but is supported by small case series and randomized trials that show that, in patients with heart failure restoring sinus rhythm (SR), the ablation catheter can be associated with significant improvement in left ventricular ejection fraction [12].

Obesity may increase the rate of AF recurrence after catheter ablation, with obstructive sleep apnea as an important potential confounder. Obesity has also been linked to a higher radiation dose and complication rate during AF ablation [13,14]. Notably, the symptomatic improvement after catheter ablation of AF in obese patients seems comparable to the improvement in normal-weight patients. In view of the potential to reduce AF episodes by weight reduction, AF ablation should be indicated to obese patients in association with lifestyle modifications that lead to weight reduction [1,15].

Technique of Radiofrequency Ablation

RFA is a minimally invasive procedure, which is performed in the electrophysiological laboratory, usually under mild sedation and only in rare cases with general anesthesia. Electrophysiology physician will perform femoral vein puncture. Subsequently, under radiological control will be introduced diagnostic and ablation catheters through the femoral vein and inferior vena cava up to the heart (in right atrium). Then the physician will puncture the interatrial septum to penetrate in this way into the left atrium, the place of entrance of the four pulmonary veins, where he identifies the most common sites of occurrence of AF. Responsible sites will be identified by a special technique of cardiac "mapping". The catheter uses radiofrequency energy (RE) to create a lesion and to block the pathologic circuit that generates AF. This procedure is called pulmonary vein isolation and is the most common procedure used in radiofrequency ablation for AF [16].

Under the same procedure, the physician can apply radiofrequency energy to an area of the right atrium, which is the cause of other arrhythmias, atrial flutter, commonly found in patients with AF. The procedure usually takes a few hours [16].

The objective of curative treatment of typical atrial flutter is to discontinue the leadership in cavotricuspid isthmus by providing a complete line of ablation, by drawing point to point of some types of successive RE and obtaining sinus rhythm. The absence of relapses is provided only in case of a complete bidirectional block. RFA for typical atrial flutter has a high success rate in more than 80% and low risk of relapse. In case of atypical atrial flutter, success of the procedure depends on the location of the circuit, and recurrences are more frequent and can even require later antiarrhythmic therapy. Also, atypical atrial flutter that is secondary to AF ablation may be difficult to treat with RFA [16].

Another procedure of RFA is circumferential ablating of left atrium, which consist in making some confluent ablative lesions around the orifice of the pulmonary veins entrance, usually grouped two by two, these two circles can be joined together or with other anatomical structures (e.g.: mitral valve ring) with additional ablation lines. These additional lines have as a purpose left atrial flutter prevention (which may occur especially if the ablation lines are incomplete). The optimal ablation procedure varies from patient to patient [16].

There is a consensus that administration of oral anticoagulation (OAC) in peri-procedural ablation is effective in preventing thromboembolic complications. This applies both to patients who have an indication for long-term OAC and in

patients with risk factors for stroke, stressing that somehow ablation increases stroke risk in peri-procedural period [17].

According to the recommendations of the 2010 Guidelines, OAC long-term therapy post-ablation is recommended in patients with a score CHA2DS2-VASc ≥2, regardless of the apparent procedural success [17]. Anticoagulation should be maintained for at least 8 weeks after ablation for all patients. The true incidence of thromboembolic events after catheter ablation has never been systematically studied and the expected stroke risk has been adopted from nonablation AF cohorts. Although observational studies suggest a relatively low stroke rate in the first few years after catheter ablation of AF, the long-term risk of recurrent AF and the safety profile of anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, OAC after catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm outcome [1].

It is not uncommon to reappear arrhythmia after ablation in the first 2-4 weeks. It may take 1-3 months for healing of postablation scars in order to check the success of the procedure. In this interval antiarrhythmic therapy may be required. Surveillance to detect recurrent AF after RFA is important, so it is recommended that the first visit to electrophysiology physician will be 3 months post-ablation, then every 6 months during the first two years [12].

Outcome of catheter ablation for atrial fibrillation

After several procedures for catheter ablation of AF was observed that better results are obtained in young patients with short episodes of AF and in the absence of structural heart disease. Sinus rhythm is found in up to 70% of patients with paroxysmal AF and in 50% of patients with persistent AF. Many patients require more than one ablation procedure to obtain rhythm control. RFA reintervention is necessary in the approximately 9-20% of patients with more modest results. It is important that before ablation procedure the patient to be well informed about the benefits and the risks.The decision to continue treatment of AF with antiarrhythmic drugs or with RFA always belongs to patient [1].

Complications of catheter ablation for atrial fibrillation

EURObservational Research Programme (EORP) determined that the average length of hospital stay of patients after RFA is 3 days [18,19]. The frequency of major complications related to RFA is less than 5%-7 % [20]. Intraprocedural death has been reported, but is rare (0.2%) [1].

Possible complications post-RFA:

- Injury to vessels, nerves, organs and surrounding tissues by manipulating instruments
- Renal damage or allergies
- Infection or bleeding at injection site
- Arterio-venous fistula on puncture site
- Complete AV block requiring pacemaker implantation (under 1%);
- Pericardial effusion, cardiac tamponade
- Stroke; pulmonary vein stenosis
- Acute coronary syndrome
- Atrio-esophageal fistula especially in circumferential atrial ablation
- Pyloric spasm and gastric hypomotility by affecting the vagus nerve during ablation [12, 21].

Conclusions

Catheter ablation is successfully used in patients suffering from symptomatic paroxysmal AF, as an alternative to drug therapy. Performed correctly by a trained and experienced electrophysiolologist, RFA allows us to get remarkable results, being possible suspension of treatment with antiarrhythmic drugs such as: amiodarone, dronedarone, flecainide, propafenone,sotalol etc. and to avoid its so well known side effects. RFA is superior to antiarrhythmic drug therapy in preventing recurrence in both persistent AF and in the paroxysmal AF.

All patients should receive oral anticoagulation for at least 8 weeks after catheter ablation. The success rate of RFA in experienced centers for paroxysmal AF exceeds 70% a year. RFA reintervention is necessary in the approximately 9-20% of patients with more modest results. The frequency of major complications related to RFA is less than 5%. The restored sinus rhythm with RFA in patients with heart failure may be associated with significant improvement in left ventricular ejection fraction.

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Traumeel S – bioregulatory approach in the treatment of inflammation

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Abstract

Background: In the treatment of inflammation, the action of widely used non-steroidal anti-inflammatory drugs (NSAIDs) is directed mainly to inhibit the synthesis of proinflammatory mediators, cell migration and proliferation, as well as to stimulate the formation of anti-inflammatory agents. These effects allow to quickly and significantly limit the severe symptoms of acute inflammation and pain. However, at the same time, NSAIDs suppress the sanogenetic mechanism of inflammation. Absence of correction of pathogenetic mechanisms of inflammation can lead to chronic inflammation and development of its complications (cicatricial changes, adhesions, contractures, etc.). Also, nonselectivity of NSAIDs contributes to the development of known side effects. And inhibitors of cyclooxygenase 2, as it became known, with excess daily therapeutic dose also cause serious side effects. New possibilities for solving this problem have already been demonstrated by the bioregulatory approach and the complex bioregulatory medicines (BRMs) created on its principles.

Conclusions: The complex bioregulatory action of the medicine Traumeel S allows to control and optimize the course of the inflammatory process wherever it is located and of any form. Its use contributes to the full completion of inflammation with the recovery of the structure and function of the tissue, reduces the risk of complications and chronic inflammation. Such characteristics, combined with good tolerability (absence of side effects characteristic to NSAIDs) make Traumeel S a simple and reliable assistant to a doctor of any specialty in the treatment of inflammatory diseases of different localization.

Key words: Traumeel S, bioregulatory approach, inflammation.

Introduction

Acute inflammation is a protective reaction of the body to infection, traumatic, postischemic, toxic, autoimmune and other affection. Its main goal is the localization of this process with the further restoration of the damaged tissue structure and its function [3]. In the treatment of inflammation, the action of widely used non-steroidal anti-inflammatory drugs (NSAIDs) is directed mainly to inhibit the synthesis of proinflammatory mediators, cell migration and proliferation, as well as to stimulate the formation of anti-inflammatory agents. These effects allow to quickly and significantly limit the severe symptoms of acute inflammation and pain. However, at the same time, NSAIDs suppress the sanogenetic mechanism of inflammation. Absence of correction of pathogenetic mechanisms of inflammation can lead to chronic inflammation and development of its complications (cicatricial changes, adhesions, contractures, etc.). Also, nonselectivity of NSAIDs contributes to the development of known side effects. And inhibitors of cyclooxygenase 2, as it became known, with excess daily therapeutic dose also cause serious side effects [1].

New possibilities for solving this problem have already been demonstrated by the bioregulatory approach and the complex bioregulatory medicines (BRMs) created on its principles. Old name – antihomotoxic medications (AHTM). Their peculiarity is the effect of ultra-small doses of components of vegetable and mineral origin that contribute to the activation of detoxification and the restoration of self-regulation processes, including in relation to the course of the inflammatory process.

Therewith, they do not suppress the natural protective and detoxifying mechanisms of the body [3, 9, 10, 17].

Among the BRMs, the BRM Traumeel S (injectable solution, ointment) showed great opportunities in the therapy of inflammatory diseases [2, 9–11, 13, 14].

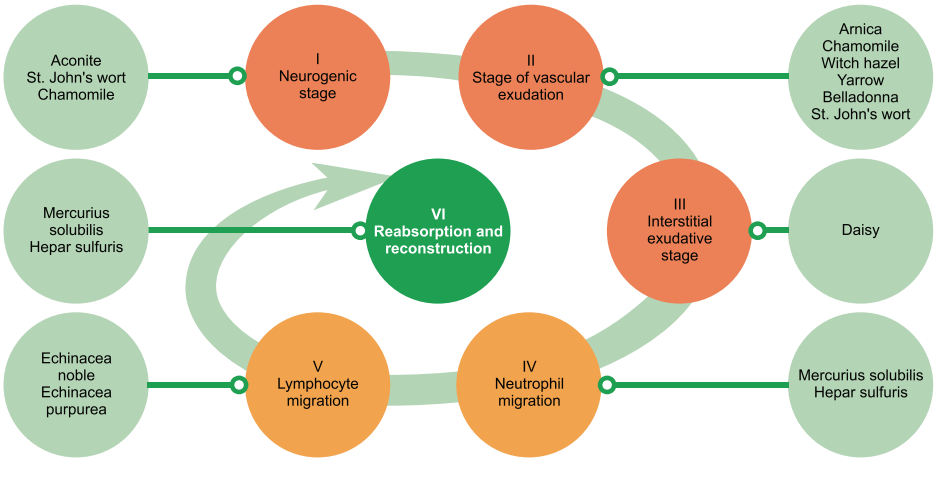

Fig. 1. Spiral-stage of inflammation – components.

Main pharmacological actions of Traumeel S: anti-inflammatory (not suppression of inflammation, but its optimization only), antiexudative, regenerating, analgesic, immunocorrecting. These properties are provided by 14 components of plant and mineral origin in ultra-small (homeopathic) doses (fig. 1).

The effectiveness of Traumeel S in inflammatory diseases is confirmed by many clinical studies conducted in Germany, Ukraine and other countries [1–17].

Traumeel S in diseases of ENT organs

Traumeel S has proven itself in the complex therapy of rhinosinusitis, otitis, tonsillitis, nasopharyngitis, both in their independent treatment and associated with the acute respiratory viral infection (ARVI), in the prevention of bacterial complications of ARVI [1-5, 7, 8, 12, 13].

Peresadin N.A. and Dyachenko T. of the Lugansk State Medical University compared the indicators of cellular and humoral immunity in children with the prescription of conventional treatment and therapy of BRM / AHTM. It was concluded that Traumeel S, in combination with other BRMs has, when used step-by-step, a clinically beneficial effect: the number of episodes of ARVI decreased 1.5-2 times, the manifestations of intoxication, headache and fever decreased; they were significantly less expressed compared with the cough control group, running nose, chest pain, sore throat. The course use of BRMs outside the aggravation period for 1-4 years indicates the potentiating and protective adaptation action of Traumeel S and other AHTMs [5, 11, 12].

Specialists from Belarus (Nikolaev V. V., Sakovich A. R., 1999) investigated the use of complex AHTMs in the treatment of acute purulent sinusitis.

The results of treatment of patients with sinusitis using the complex of BRMs (Traumeel S, etc.) and treated with classical therapy (antibiotics, antihistamines, vasoconstrictors, vitamins) were compared. The study shows that the treatment scheme for acute purulent maxillary sinusitis using BRMs is not inferior in effectiveness to conventional treatment. At the same time, a faster regression of the thermosymmetry indictors of the nasal mucosa, normalization of the pH of the nasal secretion associated with the decrease in the number of punctures in the group of patients receiving BMRs, indicates its undeniable advantages [15].

Traumeel S in pulmonology

Polish colleagues demonstrated that the use of a single Traumeel S ampoule once a week in patients with corticosteroid-dependent bronchial asthma allows lowering the daily dose of corticosteroids (triamcinolone) after five months from 4.6 to 2.6 mg, and in some patients even give up it.

It is noted that the use of Traumeel S leads to an improvement in the overall clinical condition of patients, an increase in muscle strength, and also contributes to the reduction of complications associated with prolonged corticosteroid therapy [11].

Traumeel S in nephrologic diseases

In the campus of Uzhhorod State University (Kovalchuk I.A. et al., 1999), the efficacy of BMRs in the treatment of patients with chronic pyelonephritis - Traumeel S, etc. was studied. In the main group, the BMR was used along with etiotropic drugs (antibiotics). As control was an identical group of patients who received treatment according to the standard method with allopathic drugs only. In patients of the main group, subjective improvement of the condition occurred much earlier, the laboratory indicators were faster than in the control group.

No signs of toxicity, intolerance, side effects of use of AHTM were observed [16].

Traumeel S, practical recommendations

The most informative indicator describing the presence and intensity of the inflammatory process is the concentration of the C-reactive protein (CRP) of blood serum. The increase in the level of CRP up to 3-7 mg / l already indicates local inflammation and serves as a criterion for the prescription of BMR Traumeel S. The criterion for stopping to receive Traumeel S is a decrease in the level of CRP below 3 mg / l [6].

The studies showed there has been an increase in the effectiveness of therapy for inflammation with the combination of BMR Traumeel S injections with the local (ointment) form. During the acute period, along with the course of injections, it is recommended to apply locally ointment [2, 13, 14] (table 1).

Table 1

Recommendations for the dosage of Traumeel S when combined with several dosage forms

	Acute and subacute period	Completion of treatment (2-4 weeks or more)
Basic BMR in case of inflammation (CRP level 3-7 mg/l)		
Traumeel S	2,2 ml (1 amp) i/m, s/c, i/c daily No 3-5	2,2 ml (1 amp) i/m, s/c, i/c 2-3 times (up to decrease of CRP below 3 mg / l)
	Ointment: easily to rub in/ apply under the bandage / apply on the affected area: on the 1st day – 5-6 times, then 3 times / day	Ointment: easily to rub in/ apply 2-3 times / day, incl. with massage or injected with phonophoresis No 10 (daily)

Conclusions

The complex bioregulatory action of the medicine Traumeel S allows to control and optimize the course of the inflammatory process wherever it is located and of any form. Its use contributes to the full completion of inflammation with the recovery of the structure and function of the tissue, reduces the risk of complications and chronic inflammation. Such characteristics, combined with good tolerability (absence of side effects characteristic to NSAIDs) make Traumeel S a simple and reliable assistant to a doctor of any specialty in the treatment of inflammatory diseases of different localization.

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BOOK REVIEW

Monograph "Pituitary adenomas. Morphopathology and molecular profile"

Publishing company Sirius, Chisinau, 2017, 169 pages

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Pituitary gland volume structures are neighbourhood related with important brain assemblies (the internal carotid arteries, cranial nerves III, IV, V, cavernous sinuses, optic chiasm, hypothalamus, the third ventricle, etc.) causing severe and progressive changes by local compression. Now, one plausible explanation is the absence of a detailed description regarding their biological heterogeneity, able to highlight the molecular alterations, cellular composition and susceptibility to treatment.

Despite adenomas are a sort of benign pathological entities, they can convert severe, even life threatening by local invasion and compression or by metabolic and cardiovascular complications.

Pituitary adenomas molecular features, extremely necessary to identify factors that may affect prognosis and treatment are insufficiently studied. Except GH and PRL-secreting pituitary adenomas which have been extensively studied in molecular terms, other relatively rare types that show higher aggressiveness compared to previous ones, with adverse effects on the body endocrine profile have not been fully characterized.

Research direction exhibited by the author is an innovative and current. For these reasons, this paper reports the predictive study of molecular factors and probably the therapeutic approach depending on hormonal status of pituitary adenomas and determines correlations between different molecular factors for achieving molecular subgroups, which could then be used as prognostic and especially therapeutic markers. Nevertheless, this paper contains preliminary data obtained for factors such as VEGF165b fraction inhibiting VEGF that have not been studied in pituitary adenomas until now or less and sporadically such as EG VEGF.

The study is devided into five chapters with 325 references.

The **introductory** chapter highlights the importance of recent scientific study and practice medicine.

Chapter I **Anatomy and histology.** The author describes anatomical and histological data of the human pituitary structure through the new laboratory files.

Chapter II **Pituitary adenomas: histopathology and molecular profile: Controversy and certainties** contains classic histopathological examination competed later by immunohistochemical study of hormonal profile on paraffin processed specimens.

A key importance have Chapters III **Involvement of growth factors and correspondents receptors in pituitary adenomas pathology** and IV **Predictive factors for the diagnosis and therapy of pituitary adenomas**. These subdivisions of monograph allow radical change of treatment and follow up of patients diagnosed with pituitary adenoma. Customized treatment is one of the basic switches that can give dynamic favourable results.

In Chapter V **Epidemiological data of pituitary adenomas hormonal profile in Moldova compared with those in Romania.** It is the first analysis of the pituitary adenomas structure depending on geographical area, which would allow highlighting some environmental factors involved in the aetiology of these tumors.

Conclusions: "Pituitary adenomas. Pathology and molecular profile" proposed by Dr. Eugen Melnic is well-done and current study and should be printed as a monograph. The work is intended for resident doctors, specialists in pathology, neuropathology, neurology, neurosurgery, endocrinology, oncology and molecular biology.

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